No. 23-1540

United States Court of Appeals for the Federal Circuit

AZURITY PHARMACEUTICALS, INC.,
Plaintiff-Appellant,

v.

ALKEM LABORATORIES LTD.,
Defendant-Appellee.

Appeal from the United States District Court for the District of Delaware
Case No. 1:19-cv-02100, Judge Mitchell S. Goldberg

PLAINTIFF-APPELLANT'S OPENING BRIEF

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Dated: March 22, 2023

REPRESENTATIVE CLAIMS

U.S. Patent No. 10,786,482:

Representative Claim 18:

> **14**. An oral liquid formulation comprising:
> (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
> (ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5mM and about 20 mM in the oral liquid formulation;
> (iii) about 1 mg/ml of a preservative, wherein the preservative is a mixture of parabens; and
> (iv) water;
> wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about 5±3° C.
>
> **18**. The oral liquid formulation of claim **14**, wherein the formulation does not contain mannitol.

Appx107.

U.S. Patent No. 10,918,621:

Representative Claim 7:

> **1**. A stable oral liquid formulation, consisting essentially of:
> (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
> (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;
> (iii) a preservative, wherein the preservative is a paraben or a mixture of parabens; and
> (iv) water
> wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
> wherein the formulation is stable at about 5±3° C for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

7. The stable oral liquid formulation of claim **1**, months wherein the buffer maintains the pH at about 3.3.

Appx134.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 23-1540

Short Case Caption Azurity Pharmaceuticals, Inc. v. Alkem Laboratories Ltd.

Filing Party/Entity Azurity Pharmaceuticals, Inc.

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 02/28/2023

Signature: /s/ Tung-On Kong

Name: Tung-On Kong

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
Azurity Pharmaceuticals, Inc.		CutisPharma Intermediate Holdings, Inc.

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Natalie Morgan Wilson Sonsini Goodrich & Rosati	Evan Sumner Wilson Sonsini Goodrich & Rosato	Ty Callahan Wilson Sonsini Goodrich & Rosati
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5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☐ None/Not Applicable ☐ Additional pages attached

Azurity Pharms. v. Bionpharma 21-cv-1286 (D. Del.)	Azurity Pharms. v. Bionpharma 21-cv-1455 (D. Del.)	Azurity Pharms. v. Annora 21-cv-0196 (D. Del.)
Azurity Pharms. v. Aurobindo 21-cv-1707 (D. Del.)	Azurity Pharms. v. Novitium 23-cv-0163 (D. Del.)	Azurity Pharms. v. CoreRx 8:22-cv-00784 (M.D. Fla.)

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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STATEMENT OF RELATED CASES

Under Federal Circuit Rule 47.5, counsel for Plaintiff-Appellant Azurity Pharmaceuticals, Inc. states that no appeal from the same trial court action was previously before this or any other appellate court and that no cases pending in any court or agency will directly affect this Court's decision in this appeal. Counsel also states that this Court's decision in this case may directly affect the following cases: *Azurity Pharmaceuticals, Inc. v. Bionpharma Inc.*, 21-cv-1286 (D. Del.); *Azurity Pharmaceuticals, Inc. v. Bionpharma Inc.*, 21-cv-1455 (D. Del.); *Azurity Pharmaceuticals, Inc. v. Annora Pharma Private Limited*, 21-cv-0196 (D. Del.); *Azurity Pharmaceuticals, Inc. v. Aurobindo Pharma Ltd.*, 21-cv-1707 (D. Del.); *Azurity Pharmaceuticals, Inc. v. Novitium Pharma, LLC*, 23-cv-0163 (D. Del.); *Azurity Pharmaceuticals, Inc. v. CoreRx, Inc.*, 22-cv-00784 (M.D. Fla.).

INTRODUCTION

This is a Hatch-Waxman case in which the district court found that the asserted claims of U.S. Patent No. 10,786,482 ("'482 patent") and U.S. Patent No. 10,918,621 ("'621 patent") were infringed, but held them invalid on obviousness and written description grounds. Only invalidity is at issue on appeal.

The '482 and '621 patents claim liquid formulations containing the active ingredient enalapril. Enalapril has been sold in tablet form since 1985 to treat high blood pressure. Infants and other young children afflicted with high blood pressure cannot swallow tablets or have great difficulty doing so. As a workaround, pharmacists crushed enalapril tablets and mixed the powder in liquid—a process called "compounding." But compounding left significant room for human error, guesswork, and contamination, which created a risk of inaccurate dosing. In 2013, a powder enalapril formulation became available as a kit that included a powder, a liquid, and instructions regarding how to mix them. Yet the powder too left room for human error, and it quickly expired because enalapril rapidly degrades in water—which, as with all active ingredients, made it an ineffective medicine.

Specifically, enalapril was known to degrade by hydrolysis, a chemical reaction with water. Due to hydrolysis, compounded liquid enalapril formulations were "stable" for only a handful of weeks or at most 2 or 3-months. "Stability" refers to the amount of enalapril remaining in a formulation over some time period.

Stability testing measures the amount of enalapril present when the liquid formulation is first made versus the amount present later in time. Thus, the result is stated as a percentage (*e.g.*, 90% of the original enalapril remains) at a specific time point (*e.g.*, 2-months).

The absence of a commercially available liquid enalapril formulation was noted in the prior art in 1998—thirteen years *after* the tablet was available and eighteen years *before* the invention of the '482 and '621 patents. A ready-to-use (RTU) liquid enalapril formulation—*i.e.*, one that was manufactured as a liquid and required no manipulation prior to administration—was infeasible because stability of less than 12-months does not permit manufacture, shipping, storage and delivery to the patient to occur sufficiently before the medicine expires.

The '482 and '621 patents solved the hydrolysis problem. The claimed liquid formulations contain enalapril, water, 5mM-20mM of a buffer, "a paraben or a mixture of parabens" as a preservative, and are stable—95% or more of the initial enalapril amount remains—for at least 12, 18 or 24-months when stored at refrigerated temperatures (5±3 °C). The claimed formulations provide the benefit of time—time to manufacture, ship, store, and allow the patient to consume every dose *before* it expires.

At trial, Alkem's invalidity expert, Dr. Panayiotis Constantinides, insisted that the asserted claims were obvious because a POSA could have easily modified

or optimized prior art formulations to achieve the claimed stability. Yet, he admitted he did not apply the court's claim construction for the '621 patent, and he offered no explanation—none—for how a POSA would solve the hydrolysis problem. In fact, he admitted *he was unaware that enalapril hydrolyzed in water*. Although he testified that a pH of approximately 3 would guarantee the claimed stability, that testimony was conclusory, unsupported, and squarely contradicted by the prior art (Casas) reference—which discussed a liquid enalapril formulation with a pH of approximately 3, the enalapril content of which decreased by 40% after just 3-months.

As to written description, Constantinides testified that the patents' common specification was inadequate because it lacked a specific example that matched the claims with 12-months of stability data. He said nothing more. That record is plainly inadequate under *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, which held the written description "does not demand either examples or an actual reduction to practice." 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc).

Rather than reject Alkem's defenses due to plainly insufficient evidence, and while acknowledging that the prior art did not describe the claimed stability or meet all claimed limitations, the court undertook its own flawed fact-finding mission—pursuing invalidity theories that were neither argued by Alkem nor the subject of testimony. For obviousness, the court found that a POSA would not

attempt to modify the prior art—but rather would build a new formulation from scratch. To reach that conclusion, the district court erroneously relied on (1) inventor testimony, and (2) Constantinides's irrelevant, general testimony about the drug development process—testimony that contradicted his multiple admissions that a POSA would start with a prior art formulation and modify it. This "conflat[ed] [the inventor] with those of ordinary skill in the art" (*Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1340 (Fed. Cir. 2010))—an egregious legal error—and this Court has repeatedly "rejected obviousness determinations based on conclusory and unsupported expert testimony." *TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1361 (Fed. Cir. 2019).

The court also found that pH is the only variable that a POSA would believe affects the stability of the liquid formulations, and would target a pH of 3. To reach that finding, the court relied on a publication authored by Al-Omari, which (1) Alkem presented only in connection with noninfringement and never—at any point in this action—identified as relevant to obviousness, and (2) contains data that Alkem's noninfringement expert, Dr. Barrett Rabinow, admitted are mistaken and unintelligible. Thus, the court unfairly deprived Azurity of the opportunity to rebut its relevance. *Woodrow Woods & Marine Exhaust Sys., Inc. v. Deangelo Marine Exhaust, Inc.*, 692 F.3d 1272, 1281-82 (Fed. Cir. 2012); *Hassan v.*

Stafford, 472 F.2d 88, 95 (3d Cir. 1973). The court also dismissed prior art that taught away from the claims.

The legal errors, and underlying factual errors, in the court's obviousness analysis are extensive and go far beyond these examples. The numerous errors stem from the court's effort to supplement Alkem's insufficient proof. To do that the court dismissed the testimony of record regarding the perspective of a POSA with respect to liquid enalapril formulations prior to the patented invention, and instead relied on inventor testimony and conclusory expert testimony (not specific to enalapril) to create a different view of a POSA contrary to the relevant testimony, found facts unsupported by any testimony, and ignored or expressly dismissed aspects of the prior art and consistent testimony from all witnesses showing nonobviousness.

The story is similar for written description. The district court went to great lengths in attempting to shore up Alkem's inadequate proof. The court applied this Court's precedent regarding *chemical/biological genus claims* to Azurity's *formulation claims*. As the opinion confirms, the court did not appreciate the stark differences between the claims at issue in those cases and here, and thus applied an incorrect legal standard reviewable by this Court *de novo*. Also, similar to the court's obviousness analysis, it found facts unsupported by any testimony. The opinion identifies certain excerpts from the specification as inadequate, but no

testimony addressed those excerpts at all—which confirms that the district court shifted the burden of proof to Azurity to show that written description was adequate.

The district court's invalidity rulings are plagued by multiple errors of law and should be reversed.

JURISDICTIONAL STATEMENT

Azurity appeals from the final judgment of the U.S. District Court for the District of Delaware entered on February 10, 2023. Azurity timely filed a notice of appeal on February 14, 2023. Accordingly, this Court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. Whether the district court committed legal error in holding Azurity's patent claims obvious, while failing to assess obviousness from the perspective of a POSA when it rejected the parties' consistent position "that a POSA would … modify[] the prior art" and while acknowledging that "no prior art publication had described an enalapril liquid that was stable for 12 months" or "met all limitations of any asserted claim."

2. Whether the district court incorrectly applied this Court's precedent in using genus claim precedence for the claimed formulations, leading to the erroneous conclusion that a specification that "state[d] that parabens can be used as

the preservative" and "describe[d] a formulation with all of the claimed ingredients except for paraben preservatives," instead using "a preservative that is sodium benzoate," lacked adequate written description.

STATEMENT OF THE CASE

A. Enalapril—Its History and Importance

Enalapril is an ACE inhibitor used to treat high blood pressure in adults and children. Appx1045-1046, Appx1083-1087; Appx1417. Before enalapril can treat high blood pressure, it must convert to another substance—enalapril<u>at</u>. Appx1085-1086. Enalapril<u>at</u> is not given directly to patients because it does not absorb into the blood stream when orally administered. *Id.* A patient must take enalapril, which is absorbed and then reacts with water to become enalapril<u>at</u>. *Id.*; Appx87 (1:49-53). Enalapril is thus unstable in water—a circumstance that presents a significant challenge to a POSA attempting to make a liquid formulation that is stable for more than 12-months. Appx1088-1089.

1. The pill/tablet

In 1985, FDA approved the first enalapril medication—an oral tablet. Appx976 (¶4). The tablet helped many patients, but infants, young children, and the elderly could not swallow it or had difficulty doing so. Appx1087. To treat these patients, pharmacists would "compound" enalapril tablets. *Id.*; Appx1417-1420; Appx89 (5:41-53). Compounding had significant drawbacks: it left room

for human error and contamination and came with risk of inaccurate dosing due to the variety of liquids used and the tendency of enalapril to rapidly degrade. Appx89 (5:45-50); Appx1088. Compounding was "a real barrier or problem when it came to being able to deliver appropriate … [and] consistent dosing." Appx1433.

2. The powder

In 2013, Azurity released the Epaned Kit—a first step towards addressing the problems with compounding. Appx1089-1090. The Kit included an enalapril powder and a liquid to mix with the powder. Appx1047. Once mixed (a process called reconstitution), the liquid was stable for 60 days. Appx1048, Appx1089-1090.

3. The product (Epaned® RTU)

The ideal liquid dosage form is a RTU liquid—a product manufactured and distributed as a liquid, requiring no further manipulation before administration—that lasts at least a year. Appx1090; Appx1422-1423, Appx1437, Appx1440. In 2016, Azurity developed that product—Epaned® RTU. Appx976-977 (¶¶5, 12).

B. Azurity's Patents

The '482 patent and the '621 patent—are directed to oral liquid formulations containing: about 0.6 to about 1.2 mg/ml of enalapril, between about 5 mM and about 20 mM of a buffer (the '482 claims require a specific buffer), "a paraben or a mixture of parabens" as a preservative (the '482 claims specify the concentration 1 mg/ml), and water. Appx107 (claim 14); Appx134 (claim 1). Each asserted

claim includes a stability limitation requiring that 95% or more of the initial enalapril remain at the end of at least 12-months at refrigerated temperature (5±3 °C). *Id*. The patents share a common specification.[1]

The specification repeatedly states, "[i]n some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens." Appx49 (6:35-37), Appx91 (10:35), Appx92 (12:34-36). The specification describes "embodiments" containing a "paraben" at least 13 times (Appx89 (6:35-36), Appx91 (10:35), Appx92 (12:34-39, 12:46-57), Appx92-93 (12:66-13:5)), and "embodiments" containing a "mixture of parabens" at least 11 times. Appx89 (6:36-37), Appx92 (12:36-39, 12:46-57), Appx92-93 (12:66-13:5). The specification identifies "exemplary preservatives," including at least four parabens (Appx91 (10:23-32)), and exemplary amounts of "parabens or mixture of parabens." Appx92-93 (12:34-13:7). The specification contains examples of enalapril formulations containing a paraben or mixture of parabens and 8-weeks of stability data for those examples. Appx102 (Table A-1), Appx103 (Table C-1).

The asserted claims of the '482 patent depend from claim 14 and state further limitations: sucralose as a sweetener (claim 16); the absence of mannitol (claim 18); a pH of about 3.3 (claim 22); stability of 18-months (claim 23); and a

[1] We cite only the '482 specification.

buffer concentration range of about 10 mM to about 20mM (claim 28). Appx107. Claim 1 of the '621 patent is similar to claim 14 of the '482 patent but includes the transitional phrase "consisting essentially of"—meaning the claim includes all listed ingredients and any additional ingredients "that do not materially affect the basic and novel properties of the invention." Appx828; Appx829. The asserted '621 claims depend from claim 1 and state further limitations: specific buffers (claim 4); a pH of about 3.3 (claim 7); 18-months stability (claim 17), and 24-months stability (claim 18). Appx134.

C. Alkem's Copied Formulation

Alkem's ANDA formulation is straight from column 3 of the specification substituting one disclosed preservative (sodium benzoate) for another (a mixture of parabens).

	Azurity's Claimed Formulation	**Alkem's Copied Formulation**
Enalapril Maleate	1 mg/mL	1 mg/mL
Sucralose	0.7 mg/mL	0.7 mg/mL
Citric Acid	1.82 mg/mL	1.82 mg/mL
Sodium Citrate	0.15 mg/mL	0.15 mg/mL

	Azurity's Claimed Formulation	Alkem's Copied Formulation
Preservative	1 mg/mL (sodium benzoate)	1 mg/mL (mixture of parabens)
Water	Yes	Yes
pH	Less than about 3.5	Less than about 3.5
Stability	5±3° C for at least 12-months	5±3° C for at least 12-months

Compare Appx88 (3:50-62) with Appx2361.

D. Prior Art

Nahata (1998). Nahata[2] did not show any stability longer than 3-months and did not disclose a pH near 3. Appx2239-2240. Alkem relied on it only for the statement that in 1998 there was "[n]o liquid dosage form … commercially available for pediatric patients." Appx2238; Appx1279-1280.

Allen (1998). Allen[3] studied the stability of three liquid enalapril formulations—with pHs of 4.7-4.8, 4.7-4.8, and 3.9—for 60 days. Appx2227.

[2] Nahata, et al., "Stability of enalapril maleate in three extemporaneously prepared oral liquids," Am. J. Health-Sys. Pharm., 55:1155-1157 (June 1, 1998).

[3] Allen, et al., "Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids," Am. J. Health-Syst. Pharm., 55:1915-1920 (Sept. 1998).

Allen also referenced one 90-day study where a pH 5 diluent maintained 90% of the initial enalapril and asserted that enalapril "is reported to have maximum stability at a pH of ~3." Appx2227-2229. In support, Allen cited only "the Merck Index," which said nothing about pH or the maximum stability of enalapril. *Id.*; *see* Appx17 (n.14). The Merck Index[4] did not describe enalapril formulations or reference stability at all. Appx2333-2334; *see also* Appx1361-1363.

de Villiers (2008). de Villiers[5] is a textbook chapter that stated "[t]he chemical stability of many drugs in solution may be improved by maintaining the pH of the solution in a particular range." Appx2316. de Villiers did not mention enalapril, much less discuss the best pH for stability. *Id.* Neither did de Villiers teach the claimed ranges of buffer concentration. de Villiers listed buffer types appropriate for specific pH ranges and provided some "equations useful in acid-base and buffer calculations." Appx2316-2320.

Sosnowska (2009). Sosnowska[6] reported only 30 days of stability of compounded liquid enalapril formulations. Appx2232-2233, Appx2235.

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[4] The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals (12th ed.).

[5] de Villiers, M. "Buffers and pH Adjusting Agents" (3d ed., J.E Thomson ed. 2009).

[6] Sosnowska, et al., "Stability of extemporaneous enalapril maleate suspensions for pediatric use prepared from commercially available tables," Acta Poloniae Pharmaceutica-Drug Research, 66(3):321-326 (2009).

Sosnowska used liquids with a pH of 3, citing the Merck Index. Appx2233, Appx2237. The district court found that citation was "inaccurate[]." Appx17 (n.14).

Casas (2013). Casas[7] prepared enalapril formulations with pH between 2.55 and 2.78 (which Constantinides testified is "about 3"). Appx2727, Appx2730; Appx1359-1360; Appx31. Casas performed "[t]hree month stability testing," charted the data over the first 50 days, and reported that "[a]fter 3 months … drug content of [the formulation] decreased by 40%" at all temperatures studied, including refrigerated. Appx2729, Appx2732-2733. From this, Casas "propose[d] an expiration date of 50 days." Appx2733.

'747 patent (2013). The '747 patent[8] claimed an oral enalapril solution, stable for at least 12 weeks at room temperature. Appx2288 (claim 1). The patent defined "stable" as maintaining "about 90% enalapril." Appx2279 (13:5-10). It did not disclose a buffer concentration range or identify a pH of the liquids. Some of the described liquids were "stable" (90%) for 36 weeks at "refrigerated and ambient conditions." Appx2279 (13:29-33). The '747 patent claims required mannitol, which the patent described "as a stabilizing agent" at least 50 times.

[7] Casas, et al., "Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients," Pharm. Dev. & Tech., 20(3):271-278 (Nov. 26, 2013).

[8] U.S. Patent No. 8,568,747.

Appx2288 (claim 1), Appx2275 (5:50). Data showed that the formulations with mannitol were the "most stable." Appx2284 (23:39-40).

Epaned Kit Insert (2014). The Kit Insert[9]—prescribing literature for Epaned Kit—explained that the Kit contained mannitol and other excipients. Appx2218 (§11). It did not give a buffer concentration or the pH of the liquid.

E. District Court Proceedings

Azurity sued Alkem for infringement of the '482 and '621 patents and other patents not at issue on appeal. Appx136. The USPTO issued the asserted patents over nearly all the prior art Alkem relied on. Appx981-983 (¶¶51, 54, 56-58); Appx1379.

1. Bench trial

Azurity tried its claims that Alkem infringed the '482 and '621 patents to the bench. Alkem asserted five invalidity defenses—(i) obviousness; (ii) indefiniteness; (iii) lack of adequate written description; (iv) lack of enablement; and (v) improper inventorship—but after trial, Alkem withdrew its indefiniteness, inventorship, and enablement defenses. Appx1641 (n.1); *see generally* Appx1680-1681. The court held that Alkem infringed all claims and held the patents invalid for obviousness and lack of written description.

[9] Highlights of Prescribing Information (EPANED (Enalapril Maleate) for Oral Solution (Sept. 2014)).

(a) Obviousness

At trial, Constantinides, did not understand that "hydrolysis converts … enalapril into enalaprilat" (Appx1364) even though "[i]t was … known before the present invention that enalapril can degrade in water, a fact relevant to enalapril's chemical stability." Appx17 (citing Appx1085-1086; Appx1341, Appx1467-1468; Appx2227-2228); *see also* Appx30 (n. 21). That mattered because preventing enalapril from hydrolyzing was the fundamental challenge overcome by the invention. Additionally, Constantinides testified that prior to Azurity's invention, a POSA would have modified or optimized a prior art formulation (Appx1368), not that a POSA would have designed a new formulation from scratch, and admitted that the prior art did not disclose every claim limitation. Appx1365.

i. 95% stability for at least 12-months limitation

The experts' undisputed testimony confirmed that no prior art describe a liquid enalapril formulation that is stable for anywhere close to 12-months; the closest was *3-months*. Appx1283, Appx1292, Appx1369, Appx1372-1373, Appx1380, Appx1382, Appx1388, Appx1446-1447; Appx1543, Appx1561-1562, Appx1594-1595. The testimony also highlighted that the prior art had stability targets of 90% (not 95%). Appx1541-1542, Appx1546-1547, Appx1551, Appx1560, Appx1563.

Constantinides concluded that 95% stability for at least 12-months was found in the prior art because two references "disclose[d] that there are a range in terms of the … remaining potency of the drug upon the investigated stability times" of less than 3-months and because "the FDA guidance for a drug product which is intended to be refrigerated … [is, at] minimum[,] 12 months." Appx1316-1317. Constantinides reached that conclusion while conceding that it was "not the purpose of any FDA guidance" to "explain how one of skill in the art can take an enalapril formulation and make it stable at 12 months under refrigerated conditions" (Appx1388-1389) and that a POSA could only use "accelerated stability studies" that had at least "six months" of data "to further extrapolate the 12-month stability under refrigerated conditions." Appx1308; *see also* Appx2303.

Constantinides further testified that because the stability of enalapril *powder* is measured for 12-months with a stability target of 95% in the '747 patent, a POSA could "optimize" that formula and "extend the stability to 18 months or preferably two years." Appx1320-1321; *but see* Appx1533. This testimony reflects Constantinides's fundamental lack of knowledge regarding enalapril degradation in water.

Azurity presented testimony that the stability of the claims was unexpected, objective evidence of non-obviousness. Appx1567-1570, Appx1580-1582.

ii. pH of "about 3.3" or "less than 4.5" limitation

There was testimony concerning what the prior art revealed about the effect of pH on enalapril solutions. Constantinides admitted that none of the prior art directly studied the issue and that the Merck Index—the only reference cited to support that enalapril is "maximally stable" at a pH of 3—says nothing about the pH at which enalapril is maximally stable. Appx1361-1363. He testified that "a POSA would start with the Allen reference for purposes of creating a ready-to-use formulation containing enalapril" (Appx1368) and "a POSA would think that the [4.7-4.8 pH] formulation [was] the best starting point for purposes of developing a ready-to-use formulation containing enalapril" "based on the stability that are presented," not the Allen formulation with a pH of 3.9. Appx1370; *see also* Appx1372-1374.

He agreed that the Casas study—which discussed liquid enalapril formulations with a pH of approximately 3—showed that "[a]fter three months … the[] drug content [] dropped 40%" and thus "a pH of approximately 3 did not prevent stability from crashing after 50 days." Appx1360. Little[10] concurred. Appx1567. That rapid drop was consistent with some types of degradation and showed that a POSA would view this prior art as "showing a formulation [(with a

[10] Dr. Steven Little, Azurity's expert witness regarding validity and infringement.

pH of 3)] where you see a very significant drop off in stability at three-months." Appx1567-1568.

iii. Buffer concentration, sucralose, and "no mannitol" limitations

Constantinides admitted that the prior art did not disclose the claimed buffer concentration. Appx1366, Appx1378-1379, Appx1382; *supra* at 13-15. In his view, however, a POSA could "determine the buffer concentrations" based on "well-known principles, so basic equilibrium, and the equations described in the de Villiers prior art." Appx1313. He did not explain how or why a POSA would choose particular buffer concentrations, and he never attempted to perform those calculations or demonstrate how they would lead to the claimed buffer concentrations. Appx1365-1368.

As to sweeteners, Constantinides testified that a POSA using the Kit as a starting point would not have substituted sucralose for the two sweeteners identified in the Kit Insert. Appx1317-1318, Appx1381.

As to the absence of mannitol, Constantinides testified mannitol would not be used in a liquid formulation of enalapril because "[m]annitol in general is a bulking agent, a diluent used with powder in solid dosage forms or in oral liquids." Appx1319. Little testified that "[m]annitol is not only a dry powder or a solid excipient … it can also be used in liquid formulations." Appx1538-1539.

The '747 patent states that mannitol is "a stabilizing agent" in its enalapril formulations. Appx2275 (5:50), Appx2283-2284 (22:55-24:40). Little explained that the '747 patent showed "that mixtures of this with mannitol in it were the most stable." Appx1537. He opined that a POSA would not "have removed mannitol from the kit formulation to make a ready-to-use liquid formulation" because "mannitol is discussed in the prior art as a stabilizing agent in the context of these formulations" so "the prior art is teaching somebody that you would want to use the stabilizing agent, not remove it." Appx1537-1538; *see also* Appx1577. Constantinides never testified about these teachings in the '747 patent.

(b) Written description

Alkem admits that "[t]he trial doesn't have a lot in the argument—or in the evidence that was being brought in about written description." Appx2094. The only evidence that Alkem offered was Constantinides's testimony that to meet the written description for "12-month stability at refrigerated conditions," the specification *must* contain "stability data [for] 12-months under refrigerated conditions." Appx1393. He testified similarly for 18- and 24-month stability. Appx1393-1394.

Given that understanding, Constantinides believed that the patents "lack[ed] written description" because he had "not seen statements [] in the specification where when parabens are used as preservatives you generate a formulation with

a … 12, 18, and 24-month stability." Appx1343-1344. In other words, going through the specification's "exemplary formulations," none of them included a paraben or mixture of parabens with 12-, 18-, or 24-month stability data. Appx1344-1347.

While Little agreed that the specification does not contain an example of 12-month stability data for a paraben formulation (Appx1589), he walked through the specification and identified language "describ[ing] embodiments of the invention that include parabens" and "examples of formulations that contain parabens." Appx1475-1477. He explained that a POSA would recognize information about the appropriate "weight of the parabens" from the description. *Id.* Little also testified that the specification revealed to a POSA that the stability standard of the invention was 95% and "includ[ed] 12-months, 18-months, and 24-months." Appx1477-1478. Little concluded that a POSA would recognize the claimed formulation is disclosed in the specification. Appx1606-1607. There was no other relevant evidence.

2. Post-trial arguments

The parties agreed that the relevant question for obviousness was whether a POSA, attempting to create a long-term stable liquid enalapril solution, would be motivated to "modify" or "tweak" prior art formulations of enalapril and have a reasonable likelihood of success in doing so. *E.g.*, Appx1660; Appx1702.

Indeed, Alkem described Little's "standard modifying the prior art formulations to stabilize them" as an "elegant and practical standard …—[] the one that should guide the court in deciding what POSAs would do under the circumstances before the Court." Appx1709-1711; *see also* Appx1712. Alkem bolstered that conclusion by pointing to Constantinides's "ample, consistent testimony" that a POSA would "tweak the prior art formulations to reach the claimed inventions," would "modify[] the prior art formulations to arrive at the claimed inventions," and would look to "the teachings in the references discussing enalapril formulations to modify those formulations to improve the long-term stability of those formulations." Appx1709, Appx1712-1713.

Azurity articulated a similar standard and highlighted Constantinides's testimony stating, "a POSA who used a prior art enalapril formulation as a starting point" would alter (or not) those prior art formulations. Appx1663-1664; Appx1751.

F. District Court Opinion

The court rejected the parties' description of "what POSAs would do under the circumstances." In its place, the court announced its own view of the "process by which drug formulations are developed," stating that a formulator "would start with a 'target product profile' which describes the desired characteristics of the drug." Appx14. In support, the court cited *the inventor's* testimony and

Constantinides's general testimony unrelated to enalapril. *Id.* (citing Appx1272; Appx2939).

The court then found that it was "known before the present invention that enalapril can degrade in water," and "that the stability of enalapril in water depends strongly on the pH of the solution" with "[t]wo prior art sources stat[ing] that enalapril is most stable when the pH of the solution is near 3." Appx17. The court also found that "no prior liquid form of enalapril met all limitations of any asserted claim," and "[i]n particular, no prior art publication had described an enalapril liquid that was stable for 12-months." Appx18. The court relied on a reference—Al-Omari[11]—that Alkem not only did *not* suggest rendered the claims obvious, but in fact explicitly disclaimed was prior art. Appx1178-1179.

The court acknowledged that "Al-Omari's study provides no information about long-term stable liquids," and that its "poorly labeled graph was a 'mistake.'" Appx20-21. Nevertheless, it relied on Al-Omari's conclusion from that uninterpretable data that "the rate of enalapril loss is dependent upon the solution pH." Appx21 (citing Appx2327).

In analyzing obviousness, the court first assessed the reasonable likelihood of success. The court acknowledged that "prior art publications did not

[11] Al-Omari, et al., "Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations," J. Pharm. Biomed. Anal., 25:893-902 (July 2001).

conclusively reveal whether enalapril in water at a pH near 3 could be stable for 12 to 24-months," and that "[n]o prior art reference states either that it was or was not possible to make an enalapril liquid that was 95% stable for 12 to 24-months at refrigerated temperature." Appx28. To overcome that, the court cited Constantinides's conclusory testimony that stability testing would be an "easy task" and that a pH of 3 would guarantee stability for 12, 18, and 24-months. Appx29.

The court also acknowledged both experts' testimony that "the stability data presented in Casas is not predictive of 12 months of stability," and "agree[d] with Azurity that Casas could suggest to a POSA that it was possible to make an enalapril liquid that was not stable in water at refrigerated temperature for more than 90 days even if a pH near 3 were used." Appx29-31. Still, the court "conclude[d] that Casas would not dissuade a POSA," because "a POSA could interpret Casas's mention of 40% degradation after 90 days not as the inevitable result of putting enalapril in water but as only the result of '[that] particular study.'" Appx31. Thus, "the prior art did confer a reasonable expectation that mixing enalapril with water and adjusting the pH to about 3 could result in a drug that was highly stable for a long period of time." Appx33.

Turning to motivation, the court announced that a "POSA would have been motivated to make an enalapril formulation as stable as the claims require" because

of "the requirements of distribution time and the FDA's requirements regarding shelf-life." Appx33-34.

The court then turned to whether "how" to make the claimed liquid would have been obvious. The court held that the claimed stability was obvious "because a POSA would have known how to achieve it through 'routine application of a well-known problem-solving strategy.'" *Id.* (citation omitted). In support, the court repeated the manufactured idea that a POSA would already know to target a pH of 3, relied on Al-Omari for the proposition that a formulator would immediately and exclusively focus on pH, and faulted Little for "not testify[ing] that enalapril degrades differently in the short and long term." Appx35-36. The court disregarded that the Merck Index, cited by the only two prior art references that claim enalapril is maximally stable at pH 3, does not support that statement. Appx37. It also cursorily dismissed the fact that several prior art studies "used pHs other than three," stating "those sources do not represent the formulations they describe to be ideal." *Id.*

Assessing whether it would have been obvious to a POSA to choose and combine the claimed ingredients, the court again began from its contrived assumption that "a formulator begins with the product's desired characteristics—its 'target product profile'—and proceeds by selecting ingredients to meet that goal." Appx39. According to the court, that "process of formulation provides a

motivation to combine elements needed to meet the target properties of the drug." *Id.* Thus, choosing and combining would have been obvious because it was "generally known in the prior art that enalapril could be mixed with water, that those liquids should use pH at which enalapril is stable, that a buffer could be used to maintain the pH, and that enalapril liquids should include sweeteners and preservatives" and because "the particular choices of buffers, sweeteners, and preserves claimed were individually known … to be usable with enalapril." Appx39-40. Again assuming that a POSA would not modify the prior art, the court found Azurity's argument that "a POSA would not think it obvious to make a formulation without mannitol" to be "inconsistent with how a POSA would choose ingredients." Appx42.

Considering written description, the court noted that "the specification describes a formulation with all of the claimed ingredients except for paraben preservatives," and that "the specification states that parabens can be used as the preservative." Appx47. It even acknowledged that "Azurity is correct that aspects of the invention described separately in the specification can be combined to meet all limitations in the asserted claims." Appx50. But it held that, "while a formulation meeting all claim limitations could theoretically be constructed by picking and choosing different parts of the specification," the asserted patents lack an adequate written description because the asserted claims "use 'functional

language,'" only claiming "the subset of [enalapril] liquids that are stable." Appx49-50 (citation omitted). According to the court, that foreclosed written description because "a POSA reading the specification would not know which enalapril formulations containing parabens are as stable as the asserted claims require." Appx50.

STANDARD OF REVIEW AND RELEVANT LAW

As patents are presumptively valid, both obviousness and written description must be proven by clear and convincing evidence. 35 U.S.C. § 282; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *Ariad*, 598 F.3d at 1354. This Court "retain[s] plenary review to determine whether, as a legal matter, the evidence satisfies the clear-and-convincing standard of proof." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (citing *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 993-94 (Fed. Cir. 2009) ("*P&G*")).

This Court reviews a district court's determination of obviousness de novo and its underlying factual findings for clear error. *P&G*, 566 F.3d at 993-94. The Court reviews written description findings for clear error, but exercises plenary review of the "district court's interpretation of precedent regarding the written description requirement." *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014). A finding is "clearly erroneous" when the reviewing court

is left with "definite and firm conviction" that a mistake has been made, even despite some supporting evidence. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007) (citation omitted).

ARGUMENT

I. The district court's obviousness finding is improper and erroneous.

The court's obviousness analysis is replete with legal errors. Azurity respectfully requests that the Court reverse.

A. The district court's failure to find any motivation to combine the prior art improperly rested on the path of the inventor and conflicted with the undisputed testimony about a POSA's view of enalapril formulation prior to the claimed invention.

The court rejected the only theory of obviousness that Alkem offered at trial—that a POSA would have modified the prior art to develop a stable enalapril formulation. It held a POSA would have built an enalapril formulation from scratch. That conclusion rests on two legally erroneous grounds—the testimony of the inventor, and the irrelevant, conclusory testimony of Constatinides which contradicts relevant testimony of Constatinides. The decision below should be reversed.

1. Reliance on the inventor's path is legal error.

Confusing the skill of an inventor, particularly one of extraordinary skill, with that of a POSA, is legal error. In adopting 35 U.S.C. § 103, Congress directed that whether a "claimed invention" is "obvious" must be assessed from the view of

"a person having ordinary skill in the art to which the claimed invention pertains." Thus, "[t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person of ordinary skill in the art." *KSR*, 550 U.S. at 420. This Court has explained that "[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012). Applying *KSR*, the Court has warned against "conflat[ing] [the inventors] with those of ordinary skill in the art." *Eli Lilly*, 619 F.3d at 1340; *KSR*, 550 U.S. at 420. That is what happened here.

The court's finding that a POSA would have built an enalapril formulation from scratch relied on testimony from one of the inventors, Dr. Gerold Mosher. In holding that "*a formulator would work* from a target product profile and add those ingredients required to meet it," the court pointed directly to Mosher's testimony:

> Mosher specifically testified that *a POSA* seeking to make an enalapril liquid *would not* start with the commercially available liquid Ora-Sweet and attempt to reverse engineer it because determining the effect of each of its numerous ingredients would be prohibitively complicated."

Appx40 (citing Appx1271-1272; Appx2939, Appx2971). That testimony, however, did not concern how "a formulator would work," much less what "a POSA… would not" do. Rather, Mosher was asked about his personal, general practices and responded, "typically when I would develop formulations . . . I would

formulate towards [the product] profile," requested of him. Appx2939, Appx2971. He was separately asked how a POSA would modify the prior art to reach the invention and he responded, "I'm not sure," and that the POSA would need significant work. Appx2971.

Moreover, Mosher had 30-years of post-Ph.D. experience before he reached the claimed invention (Appx2335-2341). His knowledge and credentials were far superior to that of the POSA, which the undisputed evidence defined as a person with either (1) a Ph.D. relevant to pharmaceutical science having "minimal post-degree experience" formulating products, or (2) a bachelor's degree and "at least 5 years practical experience." Appx1093. That was the only definition of a POSA proposed at trial. *See also* Appx14. As in *Eli Lilly*, "the parties do not dispute . . . the level of ordinary skill in the art," and "the record will not allow th[e] court[s] to conflate [the inventors] with those of ordinary skill in the art." 619 F.3d at 1340. Yet the court based its obviousness analysis on Mosher's personal practices and his "own path" to the invention—improperly substituting the perspective of an *inventor* for that of the *POSA*. *Otsuka*, 678 F.3d at 1296. That was error—and it exemplifies the "hindsight"-based approach (*id*.) that plagued the court's entire obviousness analysis.

2. No witness testified that a POSA would have started from scratch.

Beyond its improper reliance on the perspective of the inventor, the court erred in relying on conclusory expert testimony. That too warrants reversal, as it "is improper" to "accept . . . generalized testimony as evidence of invalidity." *Schumer v. Lab'y Comput. Sys., Inc.*, 308 F.3d 1304, 1315-16 (Fed. Cir. 2002).

This Court has "repeatedly expressed concerns that crediting such testimony risks allowing the challenger to use the challenged patent as a roadmap," thus fostering "the impermissible *ex post* reasoning and hindsight bias that *KSR* warned against." *TQ Delta*, 942 F.3d at 1361. Applying this principle, the Court has repeatedly "rejected obviousness determinations based on conclusory and unsupported expert testimony." *Id*. It should do so here.

Apart from the testimony of Mosher, the only testimony that the district court cited in concluding that a POSA would have started from scratch was irrelevant, conclusory testimony of Constantinides. Appx14, Appx40. "[F]or drug development in general," he asserted, a POSA would know "the so-called target product profile" or "key objectives in reference to the drug substance." Appx1271-1272. Then, without further explanation, he declared that "a POSA would use the information in the target product profile" "to develop" "any formulation" including "a ready-to-use oral liquid formulation of" enalapril. Appx1272-1273. That is

precisely the sort of "conclusory and unsupported expert testimony" that cannot support an "obviousness determination[]." *TQ Delta*, 942 F.3d at 1361.

Moreover, Constantinides's testimony contradicts the court's notion that POSAs rely exclusively on the target product profile, or that "drug formulators do not work by taking existing formulations and adding or deleting ingredients." Appx40. In the context of his entire testimony, Constantinides did not find referencing the target product profile and modifying prior art formulations mutually exclusive (Appx1368, Appx1369-1370)—which is why both parties argued that a POSA would "combine," "tweak," or "modify the prior art formulations." Appx1660, Appx1665; Appx1704, Appx1751, Appx1754. In short, it was legal error for the court to devise its own theory, especially given the lack of evidence underlying it. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (fact finding "without any record support showing that this [fact] would reside in the ordinar[]y [POSA]" could not support obviousness).

3. The district court's framework disregards precedent requiring motivation to combine or modify the prior art.

The court's legally erroneous finding that a POSA would have started from scratch also led it to commit the error of failing to identify any evidence of motivation to modify the prior art to arrive at the claims requiring the absence or presence of certain ingredients. *See KSR*, 550 U.S. at 418. That error affects every asserted claim of the '621 patent and claims 16 and 18 of the '482 patent.

(a) The court erred in not addressing motivation to remove ingredients from the prior art for which there is no evidence in the record.

Every asserted claim of the '621 patent contains the transitional phrase "consisting essentially of." Appx134. The court construed "consisting essentially of" to mean "including the listed ingredients and open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." Appx829. Yet, Constantinides admitted that he failed to apply the court's claim construction. Appx1354. The court erred in relying on that testimony. *Cordis Corp. v. Boston Sci. Corp.*, 658 F.3d 1347, 1357-58 (Fed. Cir. 2011) (expert testimony based on an incorrect understanding of claim construction properly disregarded); *see also Frank's Casing Crew & Rental Tools Inc. v. PMR Techs., Ltd.*, 292 F.3d 1363, 1375 (Fed. Cir. 2002).

Because of Constantinides's failure to apply the court's claim construction, the record contains no evidence that (1) a POSA would have modified prior art formulations to remove ingredients not recited in the claims; or (2) that those ingredients "do not materially affect the basic and novel properties of the invention." In Alkem's three "primary" prior art references, such ingredients include:

- Allen's Ora-Sweet® and Ora-Plus® formulation: glycerin, sodium phosphate, potassium sorbate, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, and simethicone. Appx2229 (fn. g, h).

- Allen's Ora-Sweet® SF and Ora-Plus® formulation: glycerin, xanthan gum, potassium sorbate, microcrystalline cellulose, carboxymethylcellulose sodium, and simethicone. *Id.* (fn. f, g).
- Allen's Cherry Syrup formulation: Allen does not identify the ingredients (*id.* (fn. i)) and the record does not contain such information.
- Epaned Kit Insert formulation (Ora-Sweet® SF): glycerin, xanthan gum, potassium sorbate, mannitol, and silicon dioxide. Appx2218 (§11).
- '747 patent examples: lactose, sucrose, or mannitol (as stability agents), colloidal silicon dioxide; Ora-Sweet® SF (but does not disclose the ingredients). Appx2283-2284 (22:55-23:40), Appx2285 (26:52-67), Appx2286 (27:27-28:29), Appx2287 (29:10-33).

The court ignored this lack of evidence through its flawed framework. With two exceptions—mannitol and silicon dioxide (Appx42-43), the court erroneously failed to address why a POSA would remove any of these ingredients and also whether any of them would materially affect the basic and novel properties of the invention. The record is devoid of testimony or evidence on either issue. Thus, reversal is warranted with respect to all asserted claims of the '621 patent.

(b) The court erred in finding clear and convincing evidence of motivation to modify prior art to use sucralose.

Claim 16 of the '482 patent requires the presence of sucralose as a sweetener. Appx107. All of the prior art discussed above contain sweeteners, but none are sucralose. Obviousness requires clear and convincing evidence that a POSA seeking to modify any of the prior art would have been motivated to substitute sucralose for the existing sweetener. *KSR*, 550 U.S. at 418. There is no

such evidence. On the contrary, Constantinides admitted that "a POSA using [the Kit Insert] as a starting point … would not substitute sucralose for the sweeteners that are listed." Appx1381. Because the court erroneously concluded that a POSA would not modify the prior art, it disregarded that admission and instead found that sucralose was "known to work with enalapril" and thus was a "suitable option." Appx23, Appx40-41. Those findings are not clear and convincing evidence of motivation to modify the prior art to include sucralose. Thus, reversal is warranted with respect to Claim 16 of the '482 patent.

(c) The court erred in finding clear and convincing evidence that a POSA would modify the prior art to remove mannitol.

Claim 18 of the '482 patent requires that the formulation not contain mannitol. Alkem's prior art includes the '747 patent, which repeatedly states that mannitol functions "as a stabilizing agent." Appx2275 (5:48-54), Appx2283-2284 (22:52-23:40); Appx1537-1539. Constantinides never addressed this teaching of the prior art, instead testifying only that mannitol "is not needed.". Appx1277-1278, Appx1318-1319.

In the end, none of the testimony mattered. The court dismissed the '747 patent's teaching regarding mannitol, again, because of its legally erroneous conclusion that "[a] formulator would not start with the formulation described in the '747 patent and attempt to modify it to achieve long-term stability." Appx42

(citing Appx2971). Compounding that legal error, the court credited other portions of the '747 patent as evidence of obviousness (*e.g.*, Appx31, Appx39-40, Appx41, Appx46), even though "a reference must be considered for all it t[eaches]." *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018) (citation omitted). This Court should reverse.

B. The district court erred in finding the claims obvious where the claimed buffer concentrations were not in the prior art.

Every asserted claim is limited to a buffer concentration range of "about 5 mM to about 20 mM." Appx1099-1100. Two asserted claims are further limited to "about 10 mM to about 20 mM." *Id.*, Appx1107.

Constantinides admitted that "[n]one of [the] references disclose an oral liquid enalapril formulation that used a claimed buffer concentration.". Appx1366.[12] He testified that an "optimal" buffer concentration could be "calculated" using information in de Villiers (Appx1313, Appx1326), yet never performed that calculation nor identified any optimal buffer concentration for an enalapril formulation. Appx1366-1368. Thus, the record contains no evidence that de Villiers disclosed a buffer concentration within the claimed range.

[12] This admission is among the objective reasons why the court was incorrect that "Azurity also did not seriously challenge Alkem's evidence that it was known that enalapril liquids could include buffers, preservatives, sweeteners and flavors—including the same choices for these ingredients as used in the asserted claims." Appx26-27.

Despite that absence of evidence, the district court found:

> The choice and concentration of the claimed buffer follow from the known stable pH of enalapril. Relying on de Villiers, a formulator would have selected a buffer made from sodium citrate and citric acid because de Villiers reports that such a buffer can be used at a pH near 3. And de Villiers shows that determining **an appropriate buffer concentration** for the target pH would have been routine.

Appx41 (emphasis added). That finding is demonstrably incorrect. Nothing in de Villiers evidences that the claimed buffer concentrations were "an appropriate buffer concentration" for a liquid enalapril solution that is stable for 12-months or longer. Constantinides's conclusory testimony about calculations that he did not perform is not clear and convincing evidence. *TQ Delta,* 942 F.3d at 1361.

Because every asserted claim contains the buffer concentration limitation, the absence of any evidence that a POSA would arrive at that buffer concentration warrants reversal. *Merck Sharp & Dohme B.V. v. Warner Chilcott Co.*, *LLC*, 711 F. App'x 633, 636-37 (Fed. Cir. 2017) (reversing obviousness finding because claimed concentrations were not in the prior art and testimony that the concentrations could be calculated was conclusory); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1357 (Fed. Cir. 2012).

C. The finding that pH drives stability is riddled with error.

The court's findings that pH drives the stability of enalapril in water and that the prior art taught a POSA that enalapril was most stable at a pH of about 3 likewise lack any support in the record.

1. The court's reliance on Al-Omari, a document not presented as prior art, is unfair.

Al-Omari is a significant focus of the court's obviousness analysis. Yet, Alkem never identified Al-Omari as prior art relevant to obviousness—not in any expert report and not in the Pretrial Order. Appx893-905. At trial, neither side made *any* mention of Al-Omari with respect to invalidity. The only testimony regarding Al-Omari came from Rabinow as context for his non-infringement opinion. Appx1178-1179. The court's (heavy) reliance on Al-Omari as evidence of obviousness was reversible error.

First, the court's reliance on Al-Omari violated Congress's explicit mandate that, "the party asserting invalidity … shall give notice … in writing to the adverse party at least thirty days before the trial, of the … page numbers of any publication to be relied upon … as showing the state of the art." 35 U.S.C. § 282. Congress's notice requirement may not be disregarded.

Even apart from § 282, however, Third Circuit precedent governs this issue, reading Federal Rule of Civil Procedure 37(c) to require that all disputes at trial be identified in the Pretrial Order. *Woodrow Woods*, 692 F.3d at 1281-82 (upholding a sanction to prevent use of prior art disclosed less than thirty days before trial under Rule 37(c)); *Hassan*, 472 F.2d at 95. The court's disregard for the rules is all the more troubling given Alkem's admission that Al-Omari is not relevant to obviousness. Appx1178-1179. As this Court has explained, it is legal error to rely

on a reference for obviousness when no POSA has "articulate[d] how the … reference … makes [the asserted claims] obvious." *Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1151-52 (Fed. Cir. 2004).

Because Azurity had no notice that Al-Omari could or would be considered evidence of obviousness, Azurity had no opportunity to rebut its relevance. Thus, the court's reliance on Al-Omari unfairly deprived Azurity of its adversarial right. *See Woodrow Woods*, 692 F.3d at 1280 ("[T]o protect patentees from unfair and prejudicial surprise at trial, Congress established 35 U.S.C. § 282 to provide a statutory outer limit for the disclosure of certain information relating specifically to defenses to be relied upon by an accused infringer at trial."); Appx967-969 (court stating "[t]here's not going to be any ambush or surprises" regarding prior art relied on for invalidity and Alkem's counsel stating "[t]he prior art that we're relying on in the expert report was disclosed long ago and were repeated again throughout the pretrial order.")

The court's reliance on Al-Omari also erroneously and unfairly shifted the burden to Azurity to prove non-obviousness. *See Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1382 (Fed. Cir. 2018); *see also Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012). That legal error warrants reversal because Al-Omari is essential to the flawed obviousness determination.

2. The court's reliance on Al-Omari to prove obviousness is legal error.

The court found that "Al-Omari provides a clear template for a POSA to prepare enalapril formulations at a range of pHs within the target range and test the stability of each formulation." Appx35. No testimony identifies Al-Omari as a "template" for a POSA. The "template" finding is entirely contrived. *Mintz*, 679 F.3d at 1377.

The court also erroneously relied on Figure 1 of Al-Omari, which the record reveals is unintelligible to a POSA because the Y-axis is labeled with several redundant numbers—four 2s and three 1s:

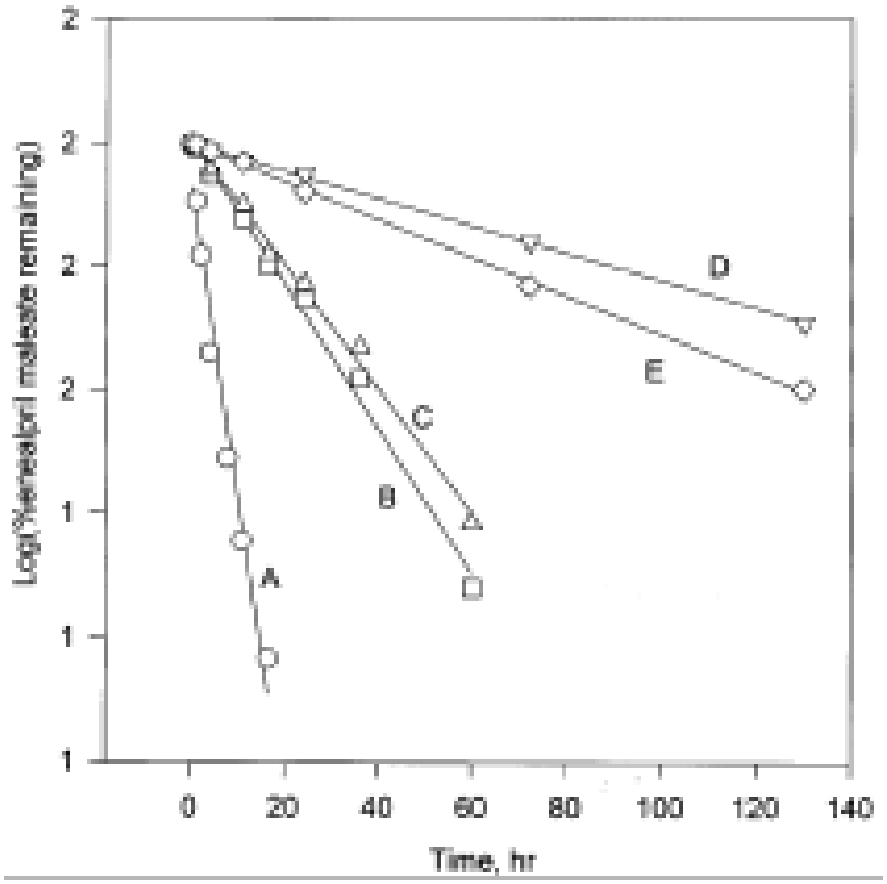

Fig. 1. Plots of log (% enalapril maleate remaining) against time for the degradation of enalapril maleate in samples of about 400 μg ml^{-1} enalapril maleate in aqueous buffers of pH 10.5 (A); 7.0 (B); 5.5 (C); 3.4 (D); and 2.2 (E) at 80°C.

Appx2327. Rabinow could only vaguely speculate about the meaning of Figure 1 and admitted that the graph is *mistaken* and that he *does not know* what the numbers in the Y-axis refer to. Appx1196-1199. "[W]here a prior art reference includes an obvious error of a typographical or similar nature that would be apparent to one of ordinary skill in the art who would mentally disregard the errant information as a misprint or mentally substitute it for the correct information, the errant information cannot be said to disclose subject matter." *LG Elecs. Inc. v.*

Immervision, Inc., 39 F.4th 1364, 1372 (Fed. Cir. 2022) (citing *In re Yale*, 434 F.2d 666, 667-69 (C.C.P.A. 1970)).

Despite this record, the court made factual findings regarding Figure 1 (Appx21) and attempted to justify them by characterizing Figure 1 as "poorly labeled and obscur[ing] the exact rate at which each study liquid degraded." *Id.* (n. 19). There is no evidence that a POSA would view Al-Omari as the court characterized, and there is zero testimony that a POSA would rely on the unintelligible information in Al-Omari for purposes of developing a liquid enalapril formulation that is stable for at least 12, 18 or 24-months. That absence of evidence mandates reversal. *See Koito*, 381 F.3d at 1151-52 . Obviousness is one area in which expert testimony has been required. *E.g.*, *Proveris Sci. Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1267 (Fed. Cir. 2008); *see also Centricut, LLC v. ESAB Grp., Inc.*, 390 F.3d 1361, 1369-70 (Fed. Cir. 2004).

3. The court erred in concluding that pH drives stability and that a POSA would have selected a pH of approximately 3 by not considering the prior art of record in its entirety.

The court also committed legal error in failing to consider evidence in Allen, viewed from a POSA's perspective, that contradicted the sweeping finding that "[t]he prior-art literature strongly conveys that pH drives the stability of enalapril in water and does not suggest that any other variable should be adjusted." Appx35. "[I]t is error to fail to consider the entirety of the art." *Arctic Cat Inc. v.*

Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1359-61 (Fed. Cir. 2017) (citing *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983)).

Allen studied the stability of three liquid enalapril formulations over 60 days at 5° C and 25° C. Appx2225, Appx2228 (Table 2). The respective pH of the formulations were 4.7-4.8 (Ora Sweet®-Ora Plus®), 4.7-4.8 (Ora Sweet® SF-Ora Plus®), and 3.9 (cherry syrup). Appx2227. Constantinides admitted that the Ora Sweet® SF-Ora Plus® (pH 4.7-4.8) "formulation ha[d] the best stability data" of the three. Appx1372-1373. There is no mention of this testimony in the opinion.

If approximately 3 is the ideal pH and pH alone drives stability, then the pH 4.7-4.8 formulation would have been the worst of Allen's formulations, not the best. The fact that the pH 4.7-4.8 formulation was the best from a POSA's perspective would inform the POSA that the components of the formulation as a whole drive stability (or lack thereof). *See* Appx1545-1546. The court erroneously ignored this teaching and, instead, cherry-picked another portion of Allen (discussed below). *Polaris*, 882 F.3d at 1069. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of

ordinary skill in the art." *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965)).

4. The evidence supporting the court's conclusion that a POSA would select a pH of approximately 3 is unconfirmed.

The court erroneously cherry-picked this statement from Allen: "[Enalapril] has pK_a values of 3 and 5.4 and is reported to have maximum stability at a pH of ~3.[18]" Appx2227, Appx2230; Appx1361-1363. Alkem's expert admitted that (1) a POSA would look to footnote 18 to see if it confirmed the content of the statement (Appx1362), (2) the document cited in that footnote—the Merck Index—says nothing about maximum stability of enalapril (Appx1362-1363; Appx2333-2334), and (3) Allen did not study the maximum stability of enalapril. Appx1361-1362. Thus, a POSA would understand the "maximum stability" statement in Allen was unconfirmed and unsupported (*see Polaris*, 882 F.3d at 1069)—which likely explains why Allen used the phrase "*reported to have* maximum stability" rather than "*has* maximum stability."

Nonetheless, the court found that "Allen provides evidence that as early as 1998, it was known in the art that a formulator seeking to make an enalapril liquid should use a pH near 3 to achieve the greatest stability." Appx20. The court acknowledged that the statement in Allen is unconfirmed and unsupported (Appx17 (n. 14)), but dismissed that because the citation was not "*inaccurate*[]"; it

was directed to another part of the sentence. *Id.* The dearth of citation for stability at a pH of 3 did not matter.

The court acknowledged that Sosnowska, the only other reference stating "[t]he maximum stability of enalapril maleate is a pH of ~ 3 (10)," "d[id] inaccurately cite the Merck Index for enalapril's stable pH." *Id.*; Appx2233. But that too did not phase the court. It simply relied on the "not inaccurate[]" citation and admittedly unsupported statement in Allen to conclude that "a POSA would not infer from the Merck Index citations that Allen was incorrect about the maximally stable pH." Appx37.

The court's failure to view Allen from a POSA's perspective was reversible legal error. *See Mintz*, 679 F.3d at 1377. The testimony is clear and undisputed: a POSA would confirm the maximal-stability statements in Allen and Sosnowska, would look to the footnote to do so, and would find the footnote lacking because the Merck Index "does not reference a pH at which enalapril is maximally stable." Appx1362-1363. Without Allen, the court's flawed finding regarding pH of 3 disintegrates.

D. No evidence supports the court's motivation to modify the prior art for the claimed stability standard of "95% or greater."

The court made the following finding:

> The FDA's guidance provides a motivation to measure stability with a 95% threshold because it defines a "significant change" as among other things "a 5% change in assay from [the drug's] initial value."

Appx33 (citing Appx2303) (alteration in original). That finding is erroneous for multiple reasons.

First, no witness testified that the FDA Guidance would have motivated a POSA to reject the 90% or greater standard in the prior art and impose the claimed 95% or greater standard. According to Constantinides, the '747 patent motivated the "95% or greater" standard (Appx1320-1321), but the '747 patent specifically identifies **90%** as the standard for stability. Appx2279 (13:5-10). The 95% standard in the '747 patent is for powders, and the court found that "a POSA would not view the stability of enalapril powder as indicative of its stability in water." Appx30 (n. 21). In the prior art, the only stated standard for stability of liquid enalapril formulations (to the extent any was stated) was 90%. Appx2279 (13:5-10); Appx1541-1542; Appx2225; Appx1546; Appx2239; Appx1560; Appx2235; Appx1563. No prior art reference used a 95% or greater standard for stability, much less over at least 12, 18 or 24-months. Appx1542.

Constantinides's testimony was that the FDA Guidance would motivate a POSA to target 12, 18 and 24-months of stability (Appx1321, Appx1329); he said nothing about the "95% or greater" standard. Thus, the court's erroneous finding is wholly unsupported. *Mintz*, 679 F.3d at 1377; *TQ Delta*, 942 F.3d at 1361.

Second, a district court "commit[s] clear error by misreading the factual content of the prior art references" (*Amazon.com, Inc. v. Barnesandnoble.com,*

Inc., 239 F.3d 1343, 1358 (Fed. Cir. 2001)), and the FDA Guidance itself confirms that the court misread it. The section cited by the court, §2.2.7.1, does not pertain to refrigerated products; instead, it addresses the "general case" that applies only "if the drug product is not specifically covered by a subsequent section." Appx2302-2303. Thus, the court erred in relying on §2.2.7.1.

The section *not* cited by the court, which *does* pertain to refrigerated products—§2.2.7.4—does not identify a target drug content after storage for 12, 18, or 24-months under refrigerated conditions. Appx2305-2306. Thus, even if the court had consulted §2.2.7.4, nothing therein would have supported the court's finding.

Third, the court erred in relying on the definition of "significant change." That term refers to events that occur during the first six-months of testing at *accelerated* conditions—*i.e.*, significantly higher temperature than refrigerated conditions. *Id.* As §2.2.7.4 explains, room temperature is an accelerated condition for a refrigerated product. Appx2305. Thus, "significant change" refers to storage *at room temperature over 6-months*. Constantinides confirmed that fact and Little's testimony is consistent. Appx1389-1390; *see also* Appx1608-1609. Thus, the court's interpretation of the FDA Guidance is contrary to all of the testimony regarding how a POSA would interpret it.

In sum, no evidence supports the notion that the FDA Guidance would have motivated a POSA to implement "95% or greater" as a stability standard for a refrigerated liquid enalapril formulation over at least 12, 18 or 24-months. The court's conclusion is clearly erroneous. *See Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 163 (Fed. Cir. 2021) (overturning PTAB decision because, in part, "The Board's reasoning finds no support in the record. The only evidence before the Board on this issue was the unrebutted testimony of Strathclyde's expert, Dr. Goodrich, who testified the opposite.").

It is also harmful. Every asserted claim requires "95% w/w or greater of the initial enalapril amount" at the end of a storage period of at least 12, 18, or 24-months under refrigerated conditions. The absence of evidence of a motivation to modify the prior art to reach the claimed stability standard warrants reversal.

E. The court relied on an improper legal standard and conclusory expert testimony to find a reasonable expectation of success while improperly dismissing prior art that taught away from the claimed invention.

1. The court erred in finding "could" and "possible" amount to a reasonable expectation of success.

The court held that the asserted claims would have been obvious because a POSA "would have expected that enalapril *could* be stable for a year or more in water at a refrigerated temperature" and the prior art "would have given a POSA confidence that long term stability was *possible*." Appx27, Appx29-30 (emphasis

added). "Possibility" is not enough. "While [this Court] afford[s] deference to a district court's factual findings … [it] retain[s] plenary review to determine whether, as a legal matter, the evidence satisfies the clear-and-convincing standard of proof." *In re Cyclobenzaprine*, 676 F.3d at 1069 (citing *P&G*, 566 F.3d at 993-94). In situations where the expert "testimony primarily consisted of conclusory references to [the] belief that [a POSA] *could* combine the[] references, not that they *would* have been motivated to do so," this Court has held that testimony "insufficient to establish obviousness by clear and convincing evidence" and reversed the court's judgment of invalidity. *InTouch Techs., Inc. v. VGo Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014).

In *KSR*, the Supreme Court highlighted two requirements of obviousness analyses that are directly relevant to this appeal. 550 U.S. at 415-16. First, a court should determine whether the invention is a combination of "old" elements. *Id.* Next, a court "*must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions," and if it is, whether that "combination of familiar elements according to known methods … does no more than yield predictable results." *Id.* at 416-17 (emphasis added). If an invention "do[es] more than yield a predictable result" that "support[s] the conclusion that [the] design was not obvious to those skilled in the art." *Id.* at 416.

Here, even taking the court's clearly erroneous findings (*supra* at 23-25) at face value, those findings do not meet the legal requirements to show obviousness. The court found that "a POSA would have expected that enalapril *could* be stable for a year or more in water at refrigerated temperature" (Appx27) and that the prior art "would have given a POSA confidence that long term stability was *possible*." Appx29-30 (emphasis added). Those findings, at most, establish that the prior art failed to rule out long-term stability, not that it made long-term stability "predictable." That *potential* of success does not reach the Supreme Court's higher threshold. To meet that, a defendant must show that the invention's combination only "yield[s] *predictable* results." *KSR*, 550 U.S. at 416.

Thus, the court erred in applying a legally incorrect standard for obviousness. That error is harmful and reversible because applying the correct legal standard to the court's "could"/"possible" findings results in only one outcome: Alkem failed to meet its burden of proof. Evidence that something is "*possible*" or that a POSA "*could*" achieve it is insufficient to establish that a POSA *would have had a reasonable expectation of that success*. Indeed, "[u]npredictability of results equates more with nonobviousness rather than obviousness." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. De C.V.*, 865 F.3d 1348, 1354-56 (Fed. Cir. 2017); *accord Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993-94 (Fed. Cir. 2017).

2. The court's "reasonable expectation of success" finding also erroneously relied on unsupported, conclusory testimony.

The court's obviousness determination also relied heavily on conclusory testimony from Constantinides. But when an "expert's testimony on obviousness was essentially a conclusory statement that a person of ordinary skill in the art would have known … how to combine any of a number of references to achieve the claimed inventions," that testimony is "conclusory[,] factually unsupported[,] … not sufficient[,] and … fraught with hindsight bias." *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012). *InTouch Techs.*, 751 F.3d at 1352. This Court should reverse.

For example, the court correctly found that "[n]o prior art reference states either that it *was or was not possible* to make an enalapril liquid that was 95% stable for 12 to 24 months at refrigerated temperature" (Appx28 (emphasis added)), but then found the prior art sufficient because "Constantinides testified that it would be an '*easy task*' to make an enalapril liquid stable for 18 or 24-months based on knowledge in the prior art" and that "a POSA would be motivated to optimize the stability of an enalapril liquid to 12, 18, preferably 24-months and *would have known how to do so*." Appx29 (emphasis added). The court's adoption of that conclusory testimony was error, particularly where, as the court recognized, "Alkem's counsel acknowledged that the prior art did not provide a 'direct road map' for making enalapril stable." The court's finding that

the prior art *did not* teach that the claimed invention was possible reflects the lack of clear and convincing evidence of a reasonable expectation of success. That should have ended the inquiry. Instead, the court "makes a burden-shifting argument," noting that the prior art also did not teach that the claimed invention was *not* possible. *Honeywell,* 865 F.3d at 1355. That burden shift is legal error: "the standard is not whether the patent owner can persuasively show that one of ordinary skill would have expected *failure*. Rather, the burden is on the" patent challenger to show that a POSA "would have had a motivation to combine the references with a *reasonable expectation of success*." *Id.* (collecting cases). In the end, a court's "reasoning that one would no more have expected failure than success is not a valid ground for holding an invention to have been obvious." *Id.* at 1356.

3. The court erred in dismissing prior art that taught away from the claimed invention.

As relevant here, Casas studied an oral liquid enalapril formulation with approximately a pH of 3 for 90 days at refrigerated temperature. Appx2729-2731; Appx1354-1355, Appx1359-1360. After 50 days "the drug content was above the 95%," (Appx2732; Appx1360) and "[a]fter 3 months … drug content of [the enalapril formulations] *decreased by 40%*." *Id*. (emphasis added).

The court disregarded Casas on the thinking that Casas did not "include[] data" showing the 40% decrease after three months. Appx28. That was error.

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir. 2003) ("[T]here can be little better evidence negating an expectation of success than actual reports of failure."). No expert testified that a POSA would disregard the statement in Casas. To the contrary, both sides' experts agreed that Casas showed that drug content crashed after 50 days:

- Constantinides admitted that the enalapril in the Casas formulation degraded by 40% after 3-months and that "a pH of approximately 3 did not prevent [the] stability [of the Casas formulation] from crashing after 50 days." Appx1360.
- Little testified that Casas showed "a very significant drop off in stability at three-months." Appx1566-1568.

Despite this unambiguous record, the court dismissed Casas: "Casas shows a graph with no visible change in enalapril concentration at pHs of 2.55 to 2.78 over 50 days refrigerated temperature (although Casas mentions, *without data*, significant degradation after 90 days)." Appx29 (emphasis added). The court also postulated that Casas's failure to plot the three-month data on a graph somehow supports disregarding it. Appx22. That postulation cannot be reconciled with the fact that both experts accepted the accuracy of Casas's three-month data. Appx1360; Appx1566-1568. This is error. *Strathclyde*, 17 F.4th at 163.

Casas presented the data in sentence form, stating: "[a]fter 3 months of study, at the three temperatures studied drug content of [the enalapril formulation] *decreased by 40%*." Appx2732 (emphasis added). The court erred in concluding

otherwise. And that error is harmful because the court's obviousness analysis failed to address the *data* in Casas showing that long term stability is *not* driven by a pH of approximately 3. Casas's *data* teach away from the court's most essential findings regarding pH by showing that a pH alone is not the only variable a POSA would consider. Casas negates any expectation of success if a POSA were to focus only on pH. Reversal is warranted.

II. The court erred in finding lack of adequate written description.

Alkem's written description defense was simple: the specification does not provide an example that matches the claims, and the specification does not provide 12-months of stability data for the claimed formulation. Appx1343-1344. Under this Court's decision in *Ariad* (among others), that theory is legally deficient on its face and should have been rejected. But the court misapplied this Court's precedent and criticized parts of the specification that no expert addressed, thus shifting the burden to prove *validity* to *Azurity* and going far beyond Alkem's inadequate proof. Moreover, the court outright ignored the undisputed evidence that Alkem's ANDA formulation is a direct copy of an embodiment in column 3 of the specification—showing that, in the real world, Alkem found the specification's written description adequate to cut and paste wholesale into its ANDA application.

A. The court incorrectly interpreted this court's precedent.

The court mistook this Court's precedent regarding *chemical and/or biological compound genus limitations* including those *that describe a genus solely by functional language*, as directly applicable to the *formulation claims* at issue here. And as a result of its "interpretation of precedent regarding the written description requirement," the court applied a heightened, incorrect legal standard that this Court "review[s] without deference" and should reverse. *Alcon*, 745 F.3d at 1190.

The court quoted *Ariad Pharmaceuticals*, 598 F.3d at 1349 as follows:

> The need for written description "is especially acute" when functional language is used. … In such a case, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."

Appx49 (citation omitted). But that analysis misapplies *Ariad*, where the claims were "genus claims[] encompassing the use of all substances that achieve the desired result of reducing the binding of [a transcription factor] to [its] recognition sites." 598 F.3d at 1341. The court incorrectly interpreted *Ariad* to mean that *all* functional claim limitations—not just functional limitations that are used to describe genus of chemical and/or biological compounds *solely* by their function—must meet a genus/species written description analysis. But no such broad rule exists, and the court's reading stretches *Ariad* beyond the breaking point. *Id.* at

1351 (explaining "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology"); *Alcon*, 745 F. 3d at 1191 (holding written description adequate for claim reciting a formulation where specification provided exemplary formulations, data for one formulation showing stability, preferred concentrations, and examples of potential formulation ingredients).

The court made a similar error in applying *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019). Appx50-51. There, as in *Ariad*, the claims encompassed a method of treating hepatitis C virus (HCV) by administering a genus of compounds having a "chemical and stereochemical structure" that "allows nearly any imaginable substituent at the 2'-down position." 941 F.3d at 1154-55. While the claims encompassed the compound that was accused of infringement (*id.* at 1163), and the specification described 18 "position-by-position formulas" within the claimed genus, these formulas did not encompass, and the specification did not otherwise describe, the compound that was accused of infringement. *Id*. at 1164-65. This Court thus held that the written description requirement was not met, explaining that "the specification provides no indication that any nucleosides *outside of those disclosed in its formulas* could be effective to

treat HCV—much less any indication as to *which* of those undisclosed nucleosides would be effective." *Id*.

Neither the claims nor the specification here are analogous to those in *Ariad* or *Idenix*. Azurity's claims encompass a liquid formulation with specified ingredients and concentrations, including parabens. *E.g.*, Appx107 (claim 16). In contrast to *Ariad*, the "parabens" limitation is a concrete one—not one described by functional language. Moreover, the formulation outlined in the asserted claims is not a claim to "a desired result," as in *Ariad*. The specification provides working and prophetic examples of the inventors' novel formulations that exhibited remarkably longer stability than anything that had come before. Appx1476-1478. In addition, the claims that the specification supports do not encompass any stable enalapril—they are defined by a specific composition that the inventors possessed when Azurity filed the priority application. Appx49; Appx102-106.

Likewise, the specification provides multiple disclosures regarding the usefulness of "a paraben" or "a mixture of parabens" as a preservative in the stable formulation of the invention, multiple prophetic and working examples of formulations that contain parabens as a preservative, and multiple examples of formulations containing 1 mg/ml of a preservative along with data showing stability (95% or more of initial drug content) for at least 12-months. Thus, the specification provides ample guidance to use a paraben as the preservative for the

claimed invention. Indeed, in contrast to the facts of *Idenix*, the court here found that the specification *does disclose* the formulation of the asserted claims—including the accused formulation. Appx50.

The court also misread *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336 (Fed. Cir. 2013). The claims there required "an alpha-amylase variant with at least the following three features: (1) a parent sequence having at least 90% homology with BSG alpha-amylase; (2) a substitution at position S239; and (3) increased thermo stability at 90° C, pH 4.5, and 5 ppm calcium." *Id.* at 1341. Regarding the specification, this Court held:

> Given the number of parent enzymes (7), the number of target positions in each of those parent enzymes (33), and the number of possible mutations at each of those target positions (at least 40), the disclosure [in the specification] spans a potentially wide range of … variants.

Id. at 1340. Thus, the specification described thousands of potential variants, "did not highlight the BSG parent or position 239 among other disclosed options," and did not "identify[] subclasses of variants that could be expected to possess the claimed properties." *Id*. at 1341-42, 1350. Under these circumstances, this Court held that the specification "lacks any indication that Novozymes had invented any thermostable alpha-amylase variants substituted at amino acid position 239 by the time of filing, much less one specifically produced from a BSG parent." *Id*. at 1349. But again, this analysis is not applicable to the claims or specification here,

which provide working examples of stable formulations and specifically identify parabens as preservatives that are expected to function in the same manner as the preservatives in the working examples.

Despite the vast disparity between the claims and specification in *Novozymes* and the claims and specification here, the court simply cut/paste a passage from *Novozymes* and substituted in the words "the claimed stability":

> Because "one could not know which, if any, individual [variants] would yield [the claimed stability] without actually making and testing the variants," stable variants containing parabens are not adequately described.

Appx51 (quoting *Novozymes*, 723 F.3d at 1350). In so doing, the court failed to meaningfully address the content of the specification through the eyes of a POSA. *Atl. Rsch. Mktg. Sys. v. Troy*, 659 F.3d 1345, 1354 (Fed. Cir. 2011).

Based on its legally erroneous analysis, the court held that the absence of 12-month stability data for an explicit, working example of the asserted claims warranted a finding that the written description requirement was not met:

> I find that all asserted claims lack written description because the specification describes a large variety of ways to combine ingredients *but does not say* which combinations that use paraben preservatives are stable. That is, if a POSA were to combine ingredients from the specification, they would not know whether they would have the claimed invention.

Appx50 (emphasis added). That analysis is squarely foreclosed by *Ariad*'s holding that "the written description requirement does not demand either examples or an

actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." 598 F.3d at 1352. By requiring the specification to contain stability data for a formulation containing parabens, the court left no room for constructive reduction to practice. And the court cited no clear and convincing evidence that a POSA reading the specification would think the inventors did not possess the substitution they taught. *Id.* at 1351.

At bottom, the court's written description analysis ignored the plain disclosures in the specification, and thus was legally flawed. This is not a chemical compound case involving a vast genus of chemical compounds described solely by functional language, undisclosed but claimed nucleosides, or thousands of potential variants. The court's application of this Court's precedent addressing those circumstances is erroneous, and the court's requirement that the specification "say" which paraben formulations have the claimed stability and show that with 12-month stability data conflicts with this Court's clear instructions to the contrary.

B. The court's factual findings lack any record support.

The written description requirement is met when the disclosure "allow[s] one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002) (citation omitted). The court correctly found that column 3

describes a formulation that meets every aspect of the claims (except parabens). Appx115 (citing '621 patent at 3:49-60). The preservative in that embodiment is sodium benzoate (1 mg/ml). And the specification provides clear guidance that sodium benzoate can be substituted with parabens as a preservative:

- "In some embodiments, the preservative is a paraben. In some embodiments, the preservative is mixture of parabens." Appx119 (12:44-48).
- "[A]bout 1 mg/ml [of parabens]." Appx119 (12:52).
- Embodiments containing a paraben or a mixture of parabens are discussed throughout the specification. Appx116 (6:37-39), Appx118 (10:35-42), Appx119-120 (12:44-17), Appx129 (Table A-1), Appx130 (Table C-1).

In sum, the specification informs a POSA that the claimed formulation can be achieved by starting with the column 3 formulation and substituting parabens for sodium benzoate. The volume of parabens (1 mg/ml) is identical to the volume of sodium benzoate (1 mg/ml). Thus, a plain reading of the specification provides more than sufficient guidance for a POSA to arrive at that combination, and Little's testimony confirmed as much. Appx1475-1478 (identifying information conveyed in specification and testifying that it conveys to a person of skill the invention of the asserted claims with reasonable clarity); Appx1606-1607 (same).

The court failed to arrive at this straightforward conclusion. Instead, it found the specification insufficient because it "does not say which other ingredients these parabens should be combined with." Appx47 (citing Appx116

('621 patent at 6:37-39)). No testimony supports that finding. On the contrary, the specification itself teaches a simple substitution that does not require any further modification of the exemplified formulations. Moreover, the court's findings are also inconsistent with each other. Appx41 ("Azurity's choice of preservative (parabens) … [was] known and known to work with enalapril."). This familiarity only confirms that a skilled artisan would appreciate the significance of the specification's express teaching. In short, the court's criticism of the specification as deficient because it "does not say which other ingredients these parabens should be combined with" is based on a flawed per se rule rather than a proper analysis from the perspective of the POSA. *Alcon*, 745 F.3d at 1192.

The court also improperly criticized the description of stability in the specification as too broad:

> Finally, with regard to the stability limitations, the specification states that "[t]he enalapril oral liquid formulations described herein are stable" under various definitions, some of which closely parallel the claim language and some of which are significantly less stringent (e.g., "for at least 1 month").

Appx47 (citation omitted). That criticism was misplaced. No witness testified about that excerpt from the specification, and the court cited no clear and convincing evidence that a skilled artisan reading the specification would think that the inventors did not possess the substitution they taught. *Ariad*, 598 F.3d at 1351.

Rather, the court erroneously substituted its own impressions for evidence regarding how a POSA would understand the specification. And Azurity was prejudiced, as it had no notice of such a contention and no opportunity to offer evidence to refute it, resulting in the court effectively shifting the burden of proof from Alkem to Azurity. *Alcon*, 745 F.3d at 1192. If that were not enough (it is), the court failed to explain how that one excerpt from the specification would have dissuaded a POSA from understanding that parabens could be substituted into the column 3 formulation. *In re Skvorecz*, 580 F.3d 1262, 1270 (Fed. Cir. 2009) (in assessing written description, the specification as a whole must be considered); *see Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308-09 (Fed. Cir. 2015).

Finally, the court made fact findings based on testimony concerning enablement while ignoring the testimony concerning written description. At trial, Little testified about the details of the specification that conveyed the formulation of the asserted claims to a POSA with reasonable clarity. Appx1475-1478. The court nowhere acknowledged this testimony. Rather, the court cited Little's testimony about whether practicing the claimed invention would require undue experimentation. Appx50-51 (citing Appx1482 (discussing lack of undue experimentation)). Indeed, the court made a factual finding that "Little acknowledged [that] a POSA seeking to determine which combinations involving

parabens are stable would 'make[e]… embodiments… and test[] them for stability.'" Appx50.

In extracting words from Little's testimony and omitting others the court badly misread his testimony about enablement:

> Q. How can you say that Dr. Mosher being able to make sodium benzoate formulations without undue experimentation supports your opinion that a person of skill could make paraben formulations?
>
> A. … [Y]ou have the specification itself, which is the context of these long-term stable formulations, you have specific parabens that are called out concentrations such that you're seeing even more information than someone would have in an obviousness analysis. So these additional declarations show that even further variations are capable of being made. They're able to be tested for stability, so there's no reason to believe that somebody would have undue experimentation in **making** these **embodiments** which are described in the specification **and testing them for stability**.

Appx1481-1482 (bolded words quoted in the Opinion). The quoted testimony concerned whether a POSA could make the claimed invention work based on the specification and without undue experimentation. It is not relevant to written description. *Alcon*, 745 F. 3d at 1191 ("[W]ritten description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described; it is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work, which is an

enablement issue.'"); *Ariad*, 598 F. 3d at 1344 (holding that written description is distinct from enablement, both in scope and purpose).

The only other testimony that the court cited in support of its holding is Little's and Constantinides's testimony that the stability data in the specification for formulations containing parabens does not extend out to 12-months or longer, and that all of the paraben examples also contain other preservatives. Appx47-51. Indeed, the only evidence that Alkem offered regarding written description was the testimony of Constantinides, who admitted that he believed written description requires the presence of a working example. Appx1393-1394. The lack of a working example is not clear and convincing evidence of inadequate written description. *Alcon*, 745 F. 3d at 1190.

CONCLUSION

For these reasons, the district court's holding that the asserted claims are invalid should be reversed.

Dated: March 22, 2023

/s/ Tung-On Kong

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Addendum

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC., ***Plaintiff*,** ***v.*** **ALKEM LABORATORIES LTD.,** ***Defendant*.**	**Civil Action** **No. 19-cv-2100**

ORDER

AND NOW, this 10th day of February, 2023, following a bench trial held on August 16, 17, and 18, 2022, and for the reasons set forth in the accompanying memorandum opinion, it is hereby **ORDERED** that **JUDGMENT** is entered in favor of Defendant and against Plaintiff on Counts VI and VII of Plaintiff's Amended Complaint.

BY THE COURT:

/s/ Mitchell S. Goldberg
MITCHELL S. GOLDBERG, J.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AZURITY PHARMACEUTICALS, INC., ***Plaintiff*,** ***v.*** **ALKEM LABORATORIES LTD.,** ***Defendant*.**	**Civil Action** **No. 19-cv-2100**

MEMORANDUM OPINION

Goldberg, J.[1] **February 10, 2023**

This lawsuit was brought under the Hatch Waxman Act for patent infringement pursuant to 35 U.S.C. § 271(e)(2)(a). Plaintiff Azurity Pharmaceuticals, Inc. ("Azurity") claims that an Abbreviated New Drug Application (ANDA) submitted by Defendant Alkem Laboratories Ltd. ("Alkem") infringes U.S. Patent Nos. 10,786,482 (the '482 patent) and 10,918,621 (the '621 patent), both titled "Enalapril formulations." Azurity asserts claims 16, 18, 22, 23, and 28 of the '482 patent and claims 4, 7, 17, and 18 of the '621 patent. Alkem denies infringement and alleges that the patents in suit are invalid due to obviousness and insufficient written description.

After presiding over a three-day bench trial, I find that Azurity has established by a preponderance of the evidence that Alkem's ANDA infringes all asserted claims. However, I also conclude that Alkem has presented clear and convincing evidence that those claims are invalid for obviousness and lack of written description. This opinion sets forth my reasons in reaching these verdicts.

[1] Pursuant to 28 U.S.C. § 292(b), I have been designated to serve as a visiting judge for the District of Delaware to handle this matter and other District of Delaware cases.

I. BACKGROUND

The patents in suit claim liquids containing the blood pressure medicine enalapril. Azurity did not invent enalapril, which had existed for decades preceding Azurity's invention. Azurity claims to have invented a way to mix enalapril with water and prevent the mixture from degrading over a period of 12 to 24 months. Alkem's ANDA is also a mixture of enalapril in water that does not degrade over 24 months.

Alkem concedes that its ANDA infringes most asserted claim limitations, disputing only two. First, Alkem contends that its ANDA does not infringe because it contains an ingredient that is not recited in any asserted claim: a "pH adjuster" added to ensure that the pH of the mixture is within a target range. According to Alkem, because none of the asserted claims recite pH adjusters, the presence of these ingredients precludes infringement of those claims that are partially closed to unlisted ingredients. Azurity responds that pH adjusters are optional in Alkem's ANDA and therefore do not affect the infringement analysis. Alternatively, Azurity argues that when a pH adjuster is added, it disappears by reacting with other ingredients in the mixture such that it is no longer present in the final liquid, thus defeating Alkem's noninfringement argument.

Alkem also contends that Azurity failed to prove that the concentration of the buffer in Alkem's ANDA is within the claimed range, again relying on the pH adjusters in conjunction with testimony from Azurity's expert Dr. Little, who opined that the pH adjusters react with citric acid to form components of the buffer. Alkem reasons that if Dr. Little's testimony is credited, the reaction he described must produce some unknown quantity of buffer, meaning there is a failure of proof that the amount of buffer left after the reaction is within the claimed range.

On the issue of validity, Alkem alleges that the asserted patent claims would have been obvious in light of the prior art and that the claims are inadequately described by the patents' written

specification. More specifically, Alkem alleges that it would have been obvious to a person of ordinary skill in the art (a POSA) to make an enalapril liquid as set out in the claims: (1) using each claimed ingredient; (2) in the claimed amounts; (3) with no other ingredients that "materially affect the basic and novel properties of the invention"; and (4) meeting the two limitations regarding the liquid being "stable" and having at least 95% enalapril with no more than 5% impurities at the end of the storage period. (See, e.g., '621 patent, Claim 4.)

While Azurity did not concede that any aspect of its invention was obvious, at trial Azurity did not dispute that the individual claimed ingredients—enalapril, water, citrate buffers, paraben preservatives, sweeteners, and flavors—were known prior to its invention. Instead, the focus of the parties' dispute is whether it would have been obvious how to combine those ingredients into a liquid that would be stable for as long as the claims require—12 to 24 months. As set forth in greater detail below, the parties offered prior studies on the tendency of enalapril to degrade in water and presented conflicting views as to what a POSA would glean from those studies about the possibility of keeping enalapril stable for 12 to 24 months.

Regarding written description, the issue is whether the patents' specification adequately describes stable enalapril liquids that contain paraben preservatives. Alkem asserts that although the specification states that parabens can be used as a preservative, it does not say which liquids containing parabens will be stable for 12 to 24 months.

II. INFRINGEMENT

A. Facts Relevant to Infringement

1. Expert Testimony

The parties stipulated that all experts were qualified, and, indeed, the background and experience of each expert was impressive. Briefly summarized, Azurity's witness Dr. Stephen Little is an expert in pharmaceutical formulation who has undergraduate and doctoral degrees in chemical engineering and has founded multiple companies engaged in pharmaceutical formulation. (N.T. 93-97.) Azurity's witness Dr. John Mahan is an expert in the treatment of young children with hypertension who holds various teaching, research, and leadership roles in pediatric nephrology. (N.T. 387-90.) Alkem's witness Dr. Barrett Rabinow is also an expert in pharmaceutical formulation who has undergraduate and doctoral degrees in chemistry and spent over 39 years as a chemist working on pharmaceutical formulations. (N.T. 177-85.) Finally, Alkem's witness Dr. Panayiotis Constantinides, also an expert in pharmaceutical formulation, has degrees in chemistry and biochemistry and has developed pharmaceutical formulations over a period of 35 years. (N.T. 244-50.)[2]

2. Asserted Claims

Azurity asserts claims 16, 18, 22, 23, and 28 of the '482 patent and claims 4, 7, 17, and 18 of the '621 patent. Claim 4 of the '621 patent is illustrative, and reads:

> A stable oral liquid formulation, consisting essentially of:
>
> (i) about 0.6 to about 1.2 mg/mL enalapril or a pharmaceutically acceptable salt or solvate thereof;
>
> (ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;

[2] These experts also offered testimony relevant to validity.

> (iii) a preservative, wherein the preservative is a paraben or a mixture of parabens; and
> (iv) water;
>
> wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;
>
> wherein the formulation is stable at about 5 ± 3° C. for at least 12 months; []
>
> wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period[; and]
>
> wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

('621 patent, Claim 4 (independent claims inserted).)[3]

3. Alkem's Accused Product

Alkem's accused product is an abbreviated new drug application (ANDA) for an enalapril liquid. It is undisputed that Alkem's ANDA contains many of the same ingredients in the same amounts as the asserted claims require, including the same active ingredient, preservative, water, and sweetener. (Amended Undisputed Facts ¶¶ 38-48; N.T. 115-16 (Little).) It is also undisputed that Alkem's ANDA meets the pH and stability limitations of all asserted claims, and that it meets the limitation of claim 18 of the '482 patent that the formulation not contain mannitol. (N.T. 118-23 (Little).)

But for two reasons, Alkem does not concede infringement. First, Alkem points to the fact that its ANDA states that pH adjusters—sodium hydroxide and hydrochloric acid—should be added in an amount "q.s." The term "q.s." means "quantum satis" or "the quantity that's necessary." (N.T. 138 (Little).) Thus, sodium hydroxide and hydrochloric acid will be added as necessary to Alkem's ANDA to achieve the target pH range. (N.T. 141, 172 (Little).) Alkem's ANDA does

[3] The parties stipulated that "no terms of the patents-in-suit require construction" and thus no hearing on claim construction was held. (ECF No. 84.)

not explicitly say whether the target pH range can be achieved without adding pH adjusters. (N.T. 173-74 (Little).) The ANDA describes "exhibit batches" of the formulation, all of which required the addition of sodium hydroxide to meet the target pH range. (N.T. 139-40, 151-52, 158-59, 164 (Little).)

The patents in suit do not claim pH adjusters, and, for that reason, Alkem argues that its ANDA does not infringe certain asserted claims. In response, Azurity's expert Dr. Little testified that sodium hydroxide (the pH adjuster) "dissociates" or splits apart in water. (N.T. 140 (Little).) In addition, when sodium hydroxide is added to the citrate buffer present in Alkem's ANDA, it reacts with citric acid. (N.T. 140-43 (Little).) For either of these two reasons, Azurity maintains that the pH adjusters are no longer present after Alkem's ANDA solution is mixed, meaning that their addition does not preclude infringement.

Alkem's second reason for asserting that its ANDA does not infringe is that Azurity has not proven that its ANDA has a buffer in the same concentration that the claims require. Alkem's ANDA specifies that a buffer should be added that consists of 1.820 mg/mL (milligrams per milliliter) of citric acid and 0.150 mg/mL of sodium citrate. (N.T. 116 (Little).) Dr. Little testified that when these numbers are converted from mg/mL to molar concentration and added together, the total is between 5 mM ("millimolar") and 20 mM, which matches the asserted claims. (N.T. 117 (Little).) But for reasons explained in more detail below, Alkem disputes that this computation shows that the buffer concentration limitation is met. Alkem points to the reaction between sodium hydroxide and citric acid Dr. Little testified to, and argues that the products of this reaction must affect the buffer concentration in some unknown way. Alkem did not offer testimony to support this argument.

B. Discussion

It is an act of patent infringement to "submit . . . an application under . . . the Federal Food, Drug, and Cosmetic Act . . . for a drug claimed in a patent or the use of which is claimed in a patent[.]" 35 U.S.C. § 271(e)(2)(A). "The patentee bears the burden of proving infringement by a preponderance of the evidence." SRI Int'l v. Matsushita Elec. Corp., 775 F.2d 1107, 1123 (Fed. Cir. 1985).

"Determining infringement requires two steps. First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process." Absolute Software, Inc. v. Stealth Signal, Inc., 659 F.3d 1121, 1129 (Fed. Cir. 2011). "For literal infringement, the patentee must prove that the accused product meets all the limitations of the asserted claims; if even one limitation is not met, there is no literal infringement." E.I. du Pont De Nemours & Co. v. Unifrax I LLC, 921 F.3d 1060, 1073 (Fed. Cir. 2019).

After considering the evidence presented at trial, I find that Azurity has proven by a preponderance of the evidence that Alkem's ANDA infringes all asserted claims. I address the two disputed claim limitations below.

1. Presence of pH Adjusters

The asserted claims of the '621 patent recite an ingredient list preceded by the phrase "consisting essentially of." By using this phrase, a patentee "signals that the invention necessarily includes the listed ingredients but is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." HZNP Medicines LLC v. Actavis Labs. UT, Inc., 940 F.3d 680, 893 (Fed. Cir. 2019) (alterations omitted). Alkem argues that this limitation is not

met because its ANDA contains pH adjusters—sodium hydroxide and hydrochloric acid—that materially affect its pH, which, in turn, impacts stability.

Azurity offers several responses. The first is that the ANDA infringes under the assumption that the pH adjusters will not be added to every batch. In Azurity's view, the designation "q.s." for the pH adjusters was a representation to the FDA that Alkem could make a compliant batch without adding the pH adjusters. (See N.T. 142-43, 151 (Little).)

To prove infringement under 35 U.S.C. § 271(e)(2)(A), Azurity must establish that if the ANDA is approved, Alkem "will likely market an infringing product." Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1570 (Fed. Cir. 1997). Where the ANDA itself "does not clearly describe a product that meets the limitations of the asserted claims," a court must look to factual evidence bearing on "[w]hat is likely to be sold, or, preferably, what will be sold." Ferring B.V. v. Watson Labs., Inc., 764 F.3d 1382, 1387-88 (Fed. Cir. 2014) (quotation marks and alterations omitted).

Azurity's assertion that the pH adjusters will not be added to every batch misreads the ANDA. The designation "q.s." means that Alkem will add as much sodium hydroxide or hydrochloric acid as needed to achieve the target pH. (N.T. 138, 207.) Whether that amount could be zero is a factual question the ANDA does not answer. (See N.T. 173-74 (Little).) As an analogy, if a recipe were to call for "1 cup of flour and enough water to make the dough hold together," it would be incorrect to read that as stating that the dough could be made without water or to say that infringement could be proven on the assumption that water would not be added.

Azurity argues that this case is analogous to Sunovion Pharmaceuticals, Inc. v. Teva Pharmaceuticals, Inc., 731 F.3d 1271 (Fed. Cir. 2013). There, Teva's ANDA permitted it to sell a range of products, some of which would infringe Sunovion's patent. Id. at 1278. The Federal Circuit held that Teva could not avoid infringement based on "internal manufacturing guidelines"

and a "declaration" that it would limit the products actually sold to ones outside the patent's scope. Id. Here, unlike in Sunovion, Alkem's ANDA does not leave Alkem free to add or not add pH adjusters at its discretion. Rather, the ANDA requires pH adjusters to be added whenever the other ingredients do not yield a pH within the specified range. (See PTX-60 at ALK_ENPL_00000402 ("Check the pH of the solution … and adjust the pH about 3.30 (ranges 3.00 to 3.60) … ."); id. at 414 ("If required adjust the pH … .").) Thus, Alkem's ANDA does not authorize Alkem to sell a range of products, some infringing and some not. And, although the ANDA is silent as to how often liquids made using the required procedure will need pH adjustment, "silence does not answer the question of infringement." See Ferring B.V., 764 F.3d at 1409.[4]

Because the ANDA does not answer the question of whether the pH adjusters will be added to every batch, Azurity "must rely on evidence" to show what product would be sold if the ANDA were approved. See Ferring B.V., 764 F.3d at 1388. Azurity offers only speculation that some batches might vary in pH such that no pH adjustment would be necessary. Contrary to Azurity's argument, I do not read Alkem's expert Dr. Rabinow's statement that sodium hydroxide is "not necessarily" added to every batch as a concession that pH adjustment is sometimes unnecessary. (N.T. 207-09.) Rather, I view this testimony only as an acknowledgment that the ANDA is ambiguous as to how often the pH adjusters will be added. For these reasons, Azurity has failed to prove that Alkem would likely market some batches of its product without pH adjusters.

[4] At oral argument, Azurity noted that Alkem's ANDA includes a proposed product label stating that the drug "may" contain sodium hydroxide and hydrochloric acid. But this statement is consistent with the ANDA's requirement to add pH adjustors whenever the pH is outside of the specified range. And, even if the word "may" in the label carried a negative inference that some units of the product would lack pH adjusters, Azurity cites no authority that Alkem would be allowed to deviate from the product's specification in the ANDA based on more permissive language in a proposed label.

Azurity next argues that pH adjusters do not matter for infringement because they do not "materially affect the basic and novel properties" of Azurity's claimed invention. Azurity notes that after the pH of Alkem's ANDA is adjusted, the final pH will always be within the ranges specified in the asserted claims. Azurity thus reasons that pH adjusters must not materially affect the pH because they do not change whether claim limitations related to the pH are satisfied. But Azurity presented no evidence that Alkem's ANDA would be stable if its pH were not adjusted. And expert testimony persuasively demonstrated that adding pH adjusters to a liquid does affect its pH, that pH affects stability, and that stability is a basic and novel property of Azurity's invention. (N.T. 149 (Little); N.T. 200-01 (Rabinow).) Therefore, I agree with Alkem that the pH adjusters, to the extent they are present, "materially affect the basic and novel properties of the invention."[5]

Importantly, however, I do accept Azurity's final alternative argument that adding pH adjusters to the mixture does not avoid the "consisting essentially of" limitation. This is because the pH adjusters are consumed and are no longer present once the solution is mixed. On this point, I credit Dr. Little's testimony that the pH adjuster sodium hydroxide is consumed when it reacts with citric acid. (N.T. 140-43 (Little).) Alkem's expert Dr. Rabinow essentially conceded that this reaction occurs and that it results in the pH adjusters being eliminated. (N.T. 211-13 (Rabinow).) The products of this reaction are water and sodium citrate, both of which are ingredients listed in the asserted claims (either verbatim or contained within the term "citrate buffer"). (See N.T. 140-43.)

While neither party requested construction of whether the claimed ingredients must be

[5] I also note that Azurity's argument that the effect of an unlisted ingredient is not "material" so long as all other claim limitations are met would make the "consisting essentially of" limitation superfluous.

present before or after mixing, claims to a mixture ordinarily go to "a composition that contains the specified ingredients at any time from the moment the ingredients are mixed together." Mars, Inc. v. H.J. Heinz Co., L.P., 377 F.3d 1369, 1374 (Fed. Cir. 2004) (emphasis deleted). Therefore, the fact that sodium hydroxide is an unlisted ingredient does not preclude infringement provided that the mixture ultimately contains only listed ingredients, and I accept Dr. Little's explanation that it does. For that reason, Azurity has proven by a preponderance of the evidence that the "consisting essentially of" limitation is met.

2. Buffer Concentration

All asserted claims require that a buffer be present in a certain concentration, such as "wherein the buffer concentration is about 5 mM to about 20 mM." ('621 patent, Claim 4 (independent claim inserted).) Alkem argues that Azurity has not proven that the ANDA contains a buffer in the same concentration. Specifically, Alkem characterizes Dr. Little's testimony that the pH adjuster sodium hydroxide reacts with citric acid to form sodium citrate as suggesting that adding pH adjusters alters the buffer concentration, a detail that Azurity's infringement testimony does not account for. As before, I will analyze the issue under the assumption that pH adjusters will be added to every batch because Azurity has not proven that Alkem would likely market a batch without them.

I credit Dr. Little's testimony that the buffer concentration in Alkem's ANDA can be determined by calculating the amounts of citric acid and sodium citrate and adding those two quantities together. (See N.T. 117 ("[Y]ou do this calculation and add them together" to obtain "the total of the buffer concentration . . . .").) I also find convincing Dr. Little's explanation that when this calculation is performed for Alkem's ANDA, the result is within the limitation recited in the claim.

Based on these facts, I conclude that the asserted buffer concentration limitations are met.

Alkem asks me to not accept Dr. Little's calculation because he also testified that added sodium hydroxide reacts with citric acid to form water and sodium citrate, which Alkem hypothesizes must "grow" the buffer. But no expert testified that this reaction grows the buffer; rather, Alkem asks me to infer it as a matter of logic. A court must not "dr[aw] on its own knowledge" of technical matters without the aid of expert testimony. See Flash-Control, LLC v. Intel, No. 2020-2141, 2021 WL 2944592, at *4 (Fed. Cir. July 14, 2021). And even if Alkem is correct that adding sodium hydroxide could change the buffer concentration, Alkem provided no reason to believe the effect is so substantial that Dr. Little should have accounted for it. For these reasons, Alkem's unsupported hypothesis that adding sodium hydroxide "grows" the buffer does not persuade me to discredit Dr. Little's otherwise convincing calculation that the buffer limitation is met.[6]

Because Azurity has proven by a preponderance of the evidence that Alkem's ANDA meets all asserted claim limitations, I conclude that Alkem's ANDA infringes all asserted claims.

III. OBVIOUSNESS

A. Facts Relevant to Obviousness

1. Background on Liquid Dosage Forms for Drugs

Azurity's claimed invention is a liquid dosage form of enalapril, which is important because not all patients can swallow pills. (See N.T. 104 (Little).) The parties' experts testified to three

[6] In light of this disposition, it is unnecessary to address Azurity's contention that Alkem forfeited its argument that the addition of pH adjusters affects the buffer concentration. However, I note that the issue in dispute is whether Dr. Little's testimony should be disbelieved because it is internally inconsistent. Given that it was Azurity's burden to present evidence of infringement and "credibility is always at issue," United States v. Green, 617 F.3d 233, 251 (3d Cir. 2010), it is unlikely that Alkem could forfeit its right to point out inconsistencies in Dr. Little's testimony.

ways that liquid dosage forms can be produced. The first is by compounding, in which a pharmacist crushes a tablet and mixes it with a liquid. (N.T. 69 (Beckloff); N.T. 104 (Little).) Compounding has drawbacks in that it creates risks of contamination and causes variation from pharmacy to pharmacy. (N.T. 105 (Little).) A second way is reconstitution, in which the drug is sold as a powder and a pharmacist mixes the powder with a liquid. (N.T. 69 (Beckloff); N.T. 106-07 (Little).) The third way is for the drug itself to be manufactured as a "ready-to-use" (or "RTU") liquid. (N.T. 107 (Little).) Ready-to-use liquids avoid the contamination issues associated with compounding. (N.T. 107 (Little).)

2. Drug Development Process

The parties agreed that a POSA would have experience developing drug formulations. (N.T. 110-11, 191.) The process by which drug formulations are developed is relevant to understanding whether Azurity's claimed invention would have been obvious before the priority date.

When developing a drug formulation, a formulator (someone who develops drug formulations) would start with a "target product profile," which describes the desired characteristics of the drug. (N.T. 258-59 (Constantinides); Mosher[7] 26.) The target product profile includes the dosage form (such as an oral liquid) and the required stability. (N.T. 259.)

Before the invention at issue, it was known in the art that stability is a critical part of the development of an oral liquid. (N.T. 259 (Constantinides).) For example, a ready-to-use liquid needs to be stable for at least 12 months to account for distribution time. (Mosher 63-64.) The term "stability" encompasses many different kinds of stability: chemical stability, physical stability, stability of taste, stability of smell, and others. (N.T. 328.) This case involves chemical stability.

[7] Citations to "Mosher" refer to Dr. Mosher's video deposition transcript.

"The chemical stability of many drugs in solution may be improved by maintaining the pH of the solution in a particular range." (DTX-1118, de Villiers[8] at 225; see also Casas[9] at 272 ("[S]ome active ingredients . . . require a certain pH range to achieve maximum stability in aqueous solution, and in such cases, the pH must be adjusted to the requirements of stability of the preparation.").) Thus, a formulator developing a drug would determine how the drug's stability depends on the pH of the formulation. (N.T. 260 (Constantinides).)

Formulators sometimes measure the stability of a drug for a short time and use that data to predict stability over a longer period, a process called "accelerated" stability testing. (N.T. 553 (Little).) Accelerated stability testing can be an "exploratory tool." (N.T. 553 (Little).) But accelerated stability testing is not always predictive of long-term stability because the way a drug degrades in the short-term can be different than the way it degrades in the long-term. (N.T. 551-52.)

The FDA has published a guidance document, dated November 2003, that "is intended to define what stability data package for a new drug substance or drug product is sufficient for a registration application . . . ." (FDA Guidance[10] § 1.1.) For drugs intended to be stored in a refrigerator, the FDA Guidance permits a registration application to use 12 months of stability data at refrigerated temperature or 6 months of stability data at an elevated temperature. (Id. § 2.1.7.2.) The FDA Guidance defines a "significant change" during testing as, among other things, "[a] 5 percent change in assay from [the drug's] initial value." (Id. § 2.2.7.1.)

[8] de Villiers, "Buffers and pH Adjusting Agents" (3d ed., J.E Thomson ed. 2009) ("de Villiers").

[9] PTX-78, Casas et al., "Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients," Pharm. Dev. & Tech., 20(3):271-78 (Nov. 26, 2013) ("Casas").

[10] DTX-1109, "Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products," United States Food and Drug Administration ("FDA Guidance").

3. Buffers

Buffers are used to maintain pH, and their use was basic knowledge for a POSA as of the priority date. (N.T. 192 (Rabinow); N.T. 257 (Constantinides).)

Alkem's expert Dr. Constantinides, Azurity's employee Dr. Mosher, and the published source de Villiers provided consistent information about how a POSA would choose a buffer for a drug, taking into account information such as the desired pH, among other factors (such as the buffer's "pK_a"). (See Mosher 33-35.) de Villiers suggests buffer types appropriate for specific pH ranges, with a citrate buffer being appropriate for a pH of 2.5 to 6.5. (de Villiers at 225-29.) A formulator will also usually have experience with many buffer systems and may rely on experience to choose one. (Mosher 58-59.)

Once the type of buffer is selected, the concentration of the buffer needs to be chosen. The buffer concentration can be determined using well-known chemical principles such as those described in the literature. (N.T. 291-94 (Constantinides, citing de Villiers).) The literature includes example concentrations of citric acid and sodium citrate that can be used to make a buffer suitable over a pH range from 2.5 to 6.5 (de Villiers at 228-30.)

4. Enalapril

Enalapril is a drug used to treat hypertension (high blood pressure). (N.T. 100 (Little).) Before enalapril can affect blood pressure, it must be converted to another chemical called "enalaprilat." (N.T. 100-01 (Little).) But because enalaprilat is not absorbed by the body, the drug that is administered to the patient must be enalapril, which then converts to enalaprilat in the body. (N.T. 103 (Little).)

The reaction that converts enalapril to enalaprilat is called "hydrolysis," and, when enalapril

is mixed with water, it can undergo hydrolysis even when it is not in the human body. (N.T. 100-02 (Little).) It was thus known before the present invention that enalapril can degrade in water, a fact relevant to enalapril's chemical stability. (N.T. 102-03, 454-55 (Little); N.T. 328; Allen[11] at 1917-18.)

It was also known in the art that the stability of enalapril in water depends strongly on the pH of the solution. (N.T. 202 (Rabinow); Allen at 1917-18; Al-Omari[12] at 898.) Thus, a formulator seeking to make an oral liquid formulation of enalapril could increase its stability by using an appropriate pH. (Allen at 1918.)

Two prior art sources state that enalapril is most stable when the pH of the solution is near 3. (Allen at 1917; Sosnowska[13] at 322.) These prior-art teachings are important because a central point in dispute is whether a POSA would have known how to make enalapril stable before Azurity's invention.[14]

The parties' experts disagreed how easy it would have been before Azurity's invention to make enalapril stable in water. Alkem's expert Dr. Constantinides testified that it would have

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[11] DTX-1074, Allen et al., "Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids," Am. J. Health-Syst. Pharm., 55:1915-1920 (Sept. 1998) ("Allen").

[12] DTX-1144, Al-Omari et al., "Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations," J. Pharm. Biomed. Anal., 25(5-6), pp. 893-902 (July 2001) ("Al-Omari").

[13] DTX-1077, Sosnowska et al., "Stability of extemporaneous enalapril maleate suspensions for pediatric use prepared from commercially available tables," Acta Poloniae Pharmaceutica-Drug Research, 66(3):321-26 (2009).

[14] Azurity argued at trial that one or both of these publications may inaccurately cite enalapril's stable pH to another source, The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals (12th ed.) (the "Merck Index"). In context, it appears that Allen's citation to the Merck Index corresponds to other information in the same sentence (enalapril's "pK_a values") and does not inaccurately cite the Merck Index for enalapril's stable pH. Sosnowska, on the other hand, does inaccurately cite the Merck Index for enalapril's stable pH.

been "easy" for a POSA to make enalapril in water 95% stable for 24 months at refrigerated temperature through "routine experimentation" based on what was known in the prior art. (N.T. 315-16.) Azurity's expert Dr. Little opined that a formulator would not consider stability for 18 months an achievable goal. (N.T. 486, 532.) In Dr. Little's view, "all of the various things in the formulation" are needed to achieve long-term stability, and, therefore, if a POSA attempted to "optimize" an enalapril liquid for stability, any alteration to the formulation could have undesirable effects. (N.T. 500, 526-27.) According to Dr. Little, Azurity managed to make enalapril stable in water by finding a "specific combination of things" that avoids "all of the different reactions that could potentially happen with" enalapril in water. (N.T. 533.)

5. Enalapril Liquid Formulations Predating Azurity's Invention

The priority date of the asserted patents is March 18, 2016. (Revised (8/14/2022) Uncontested Facts ¶¶ 15, 28.) Prior art publications consist of those that were published and publicly accessible before that date. See VidStream LLC v. Twitter, Inc., 981 F.3d 1060, 1066 (Fed. Cir. 2020).

Liquid dosage forms of enalapril had been developed prior to Azurity's invention, although no prior liquid form of enalapril met all limitations of any asserted claim. (See N.T. 352 (Constantinides).) In particular, no prior art publication had described an enalapril liquid that was stable for 12 months. (See N.T. 352 (Constantinides).) The liquid dosage forms of enalapril that had been developed before Azurity's invention are summarized below.

Nahata (June 1998) Nahata describes a study "to determine the stability of enalapril maleate" in various liquids at refrigerated and room temperature.[15] (Nahata[16] at 1156.) Nahata notes that this work was undertaken because there was "limited data on the stability of enalapril in extemporaneously prepared oral liquids" and, in particular, "no known stability data for enalapril in readily available vehicles . . . ." (Id. at 1155-56.)

Nahata studied enalapril in: (1) water, (2) a citrate buffer solution, and (3) a mixture of the commercially available liquids Ora-Plus and Ora-Sweet. The pHs of these liquids are, respectively, 7.1, 5.1, and 4.7. (Nahata at 1156.) pH is important to the obviousness analysis because enalapril was reported to be more stable at some pHs than others. As noted above, enalapril was known to be most stable at a pH near 3, and Nahata's Ora-Plus and Ora-Sweet mixture is closest to this value.

Nahata reports data on the stability of the three studied enalapril liquids. Nahata evaluates stability by measuring how much enalapril remains in the liquid over time. The data for the Ora-Plus and Ora-Sweet mixture at refrigerated temperature start at 100.0 plus-or-minus 3.6% at the beginning of the study and end at 95.8 plus-or-minus 5.9% after 90 days, with a visible downward trend in between. (Nahata at 1156.)

Allen (Sept. 1998) Allen reports on a study of liquid forms of various drugs, including enalapril. Like Nahata, Allen studied enalapril in three different liquids: (1) a mixture of Ora-Sweet and Ora-Plus, (2) a mixture of Ora-Sweet SF and Ora-Plus, and (3) cherry syrup. The pHs of these liquids are 4.7-4.8, 4.7-4.8 again, and 3.9. As noted, Allen states that enalapril is most

[15] Refrigerated temperature is 5 plus-or-minus 3 °C. (N.T. 548 (Little).)

[16] DTX-1078, Nahata et al., "Stability of enalapril maleate in three extemporaneously prepared oral liquids," Am. J. Health-Sys. Pharm., 55:1155-57 (June 1, 1998) ("Nahata").

stable at a pH near 3, and the pH of the cherry syrup liquid is closest to this value. (Allen[17] at 1918.)

Allen tested the stability of those three enalapril liquids and reports the resulting data. The study runs for a period of 60 days. Some of the tests are done at refrigerated temperature. The reported stability numbers for the cherry syrup liquid at refrigerated temperature start at 97.2 plus-or-minus 1.0% and end at 97.0 plus-or-minus 1.1%. (Allen at 1918.)

Allen also discusses prior work on the stability of enalapril and notes that a prior study found that enalapril liquids with pHs of "2 and 5 were stable for 262 and 114 days, respectively," at room temperature. (Allen at 1917-18.) Another study mentioned by Allen found that enalapril in a citrate buffer with a pH of 5 was stable for 90 days at refrigerated temperature but not as stable at room temperature. (Id. at 1918.) Regarding those prior studies, Allen observes that "[t]hose liquids were buffered to a pH that was 2 units less acidic than the pH at which the drug has maximum stability." (Id. at 1918.) In contrast to those studies, Allen's enalapril liquids use pHs "somewhat closer to the pH for maximum stability"—i.e., 3. (Id. at 1918-19.) Thus, Allen provides evidence that as early as 1998, it was known in the art that a formulator seeking to make an enalapril liquid should use a pH near 3 to achieve the greatest stability.

Al-Omari (2001) Al-Omari's study provides no information about long-term stable liquids but was offered by Alkem to demonstrate the importance of pH in making enalapril stable. Al-Omari's primary aim was to study the stability of enalapril in tablets, but Al-Omari's publica-

[17] DTX-1074, Allen et al., "Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids," Am. J. Health-Syst. Pharm., 55:1915-1920 (Sept. 1998) ("Allen").

tion contains information about enalapril liquids as well. (Al-Omari[18] at 893.) Al-Omari studied enalapril liquids with pHs of 10.5, 7.0, 5.5, 3.4, and 2.2. Stability data for each of these liquids are presented in a graph showing how fast each liquid degraded over time. This data was collected at 80 °C for under 140 hours (that is, substantially warmer than refrigerated temperature and substantially shorter than one year). (Al-Omari at 898.)

Al-Omari's graph shows that the enalapril liquid with a pH of 3.4 degraded the slowest among the liquids tested. The liquid with a pH of 2.2 was the next slowest. (Al-Omari at 898; N.T. 196-97 (Rabinow).) Al-Omari concludes from these data that "the rate of enalapril loss is dependent upon the solution pH and it is obvious that the degradation at pH 10.5 is more significant than that at lower pH values." (Al-Omari at 898.) Al-Omari also notes that a prior study had found that the rate at which enalapril degrades "depend[ed] upon [the] pH of the solution[.]" (Id. at 894.) Alkem thus offers Al-Omari to support its expert Dr. Rabinow's opinion that pH was known to be the "dominant" driver of the stability of enalapril. (N.T. 195-97, 202 (Rabinow).)[19]

Sosnowska (2009) The purpose of Sosnowska's study was to examine enalapril liquids "prepared from commercially available tablets" by compounding. (Sosnowska at 321 (abstract).) According to Sosnowska, "[i]t is important that the drug should be stable in the vehicle for the proposed duration of storage and administration of the product." (Id. at 321.)

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[18] DTX-1144, Al-Omari et al., "Effect of the drug-matrix on the stability of enalapril maleate in tablet formulations," J. Pharm. Biomed. Anal., 25(5-6), pp. 893-902 (July 2001) ("Al-Omari").

[19] At trial, Azurity pointed out that Al-Omari's graph is poorly labeled and obscures the exact rate at which each studied liquid degraded. (Al-Omari at 898.) Although Alkem's expert Dr. Rabinow relied on Al-Omari for its teaching about the relationship between pH and stability, Dr. Rabinow conceded that Al-Omari's poorly labeled graph was a "mistake." (N.T. 214 (Rabinow).) But Dr. Rabinow pointed out that, even though the exact rate at which each liquid degraded is unclear, he could tell that some of the liquids degraded at least "tenfold . . . , perhaps more." (See N.T. 214-15 (Rabinow).)

Sosnowska studied enalapril liquids that all had a pH of 3—the value Sosnowska and Allen give for the pH at which enalapril is most stable. Sosnowska's liquids used citric acid as a buffer to maintain this pH. (Sosnowska at 322.) Stability data for Sosnowska's enalapril liquids are reported. Sosnowska tested these liquids for 30 days, some at refrigerated temperature. (Id. at 322.) The average stability after 30 days was at least 98% under all studied conditions. (Id. at 322.)

Casas (Nov. 2013) Casas's objective was to develop enalapril liquids that could be made by compounding and administered to children. (Casas[20] at 271.) To achieve that objective, Casas prepared solutions of enalapril in water and measured the stability of these solutions at various temperatures. The solutions had pHs in the range of 2.55 to 2.78. (Id. at 275.) According to Casas, these liquids are ones that "a Pharmacist could easily prepare with available and low cost materials . . . ." (Id. at 272.) Casas also states that paraben preservatives should not be used in these formulations because parabens can cause allergic reactions, especially in infants, newborns, and toddlers. (Id. at 272.)

Casas presents data on the stability of the studied liquids in a graph. At refrigerated temperature, the graph shows no visible change in the amount of enalapril remaining over the 50 days of study. (Casas at 278.) But Casas also states, without corresponding data or points on the graph, that "[a]fter 3 months of study, at the three temperatures studied drug content of [the formulation] decreased by 40%." (Id. at 277.)

[20] PTX-78, Casas et al., "Physicochemical stability of captopril and enalapril extemporaneous formulations for pediatric patients," Pharm. Dev. & Tech., 20(3):271-78 (Nov. 26, 2013) ("Casas").

The Epaned Kit and the '747 Patent (Oct. 2013) The next prior liquid formulation of enalapril is Azurity's own "Epaned Kit" product. Prior to inventing a ready-to-use enalapril liquid, Azurity marketed the Epaned Kit, which consisted of an enalapril powder and a liquid (the "diluent") that could be combined to make an enalapril liquid. (N.T. 64-65 (Beckloff).)

Azurity's patent related to the Epaned Kit is U.S. Patent No. 8,568,747 (the '747 patent), which was published on October 29, 2013, and claims enalapril powders that are reconstituted into oral liquids. (See DTX-1094, '747 patent, claim 1.) The '747 patent states that some of the described liquids are "stable" for 36 weeks at "refrigerated and ambient conditions." The patent defines "stable" as "having at least about 90% enalapril and 5% or less total impurities or substances at the end of a given storage period." (Id., col. 13:5-33.) The '747 patent reports stability data for some example reconstituted liquids measured over 12 weeks, including some tests at refrigerated temperatures. The data at refrigerated temperature consistently show at least 95% of the enalapril remaining over the 12 weeks of study. (Id., col. 23.)

Relevant to some of the specific ingredients recited in the asserted claims, the '747 patent includes example liquids in which the concentration of enalapril is 1.0 mg/mL and describes the use of paraben preservatives with an enalapril liquid that is described as "stable." ('747 patent, cols. 5:28-32, 7:51-59, 22:59.) It also describes the use of sweeteners in these enalapril liquids, including sucralose and xylitol. (Id., cols. 7:60-8:37.)

Kit Insert (2014) Azurity's prescribing literature for the Epaned Kit included a document the parties referred to as the "Epaned Kit Insert," which is dated September 2014. (DTX-1073.) The Kit Insert contains information about the composition of the powder and liquid used to make the Kit. It states that the Epaned Kit uses Ora-Sweet SF as the liquid, which contains citric acid

and sodium citrate that are described as a "buffer[]." (Kit Insert § 11.) It also states that Ora-Sweet SF contains methylparaben and propyl paraben and gives the amounts of these ingredients. (Id.) Dr. Constantinides testified that the amount of preservative stated in the Kit Insert is very close to the concentration of preservative recited in the asserted claims. (N.T. 301-02 (Constantinides).)

The Kit Insert further states that the Kit powder contains mannitol, a fact Azurity offered in an effort to show that an enalapril liquid made without mannitol (as some asserted claims require) would not have been obvious. Mannitol is a "bulking agent" used in powders. (N.T. 265, 306 (Constantinides).) According to Alkem's expert Dr. Constantinides, a POSA attempting to make a long-term stable solution of enalapril in water would not try adding mannitol because it is not needed. (N.T. 265.) Azurity's expert Dr. Little disagreed and stated that mannitol has uses in liquid formulations, including as a sweetener and as a "tonicity agent." (N.T. 492-93.) Dr. Little also testified that mannitol can be used as a "stabilizing agent." (N.T. 492.)

6. Issues with Prescribing Enalapril to Children Before the Present Invention

Azurity presented evidence that before the Epaned Kit became available, physicians prescribing enalapril to children would use compounding, a practice with numerous drawbacks. Azurity also attempted to show that there were drawbacks to using its own Epaned Kit product, although for the reasons explained below, that testimony was largely speculative.

As of 2014, enalapril was the only anti-hypertensive drug that was usable by a broad age range of patients. (N.T. 403-04 (Mahan).) Given the lack of alternatives, Azurity's expert Dr. Mahan prescribed enalapril to children before there was a liquid form available, coming up with work-arounds when patients could not swallow pills. (N.T. 404-05.) As described above, some of these work-arounds, such as compounding, created safety risks.

Azurity's Epaned Kit was an improvement over compounding, leading Dr. Mahan to use the Kit over compounding. (N.T. 422-23.) The Kit became available in 2013 and was safe and effective. (N.T. 439 (Mahan).) Even with the Kit, Dr. Mahan was still concerned that pharmacies might make mistakes because many steps were involved in reconstitution. Dr. Mahan sometimes suspected that pharmacies made errors with reconstitution. (N.T. 423-25.) Azurity's head of research and development Mr. Beckloff also testified that he believed pharmacy technicians sometimes made errors with the Kit, including using the wrong diluent, poking a pen through the seal, and causing contamination with fibers from the pharmacist's sweater. (N.T. 65-66.)

But Dr. Mahan could not identify a specific instance in which a pharmacy reconstituted the Kit incorrectly. He had only heard "stories." (N.T. 440-43.) Mr. Beckloff testified that an error that resulted in a liquid of the wrong concentration would have "safety implications," but did not testify that any such error occurred. (N.T. 66.)

B. Discussion—Obviousness

"A patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. The accused infringer bears the burden of proving invalidity by clear and convincing evidence. Microsoft Corp. v. i4i Ltd. Partnership, 564 U.S. 91, 95 (2011). The obviousness inquiry is "flexible" and "functional." KSR Int'l Co. v. Teleflex Inc. 550 U.S. 398, 415 (2007). "[A] court can take account of the inferences and creative steps that a [POSA] would employ." Id. at 418. But analysis based on hindsight is forbidden. Insite Vision Inc. v. Sandoz, Inc., 783 F.3d 853, 859 (Fed. Cir. 2015). An

invention is not obvious merely because it is "sufficiently simple to appear obvious to judges after the discovery is finally made." Outside the Box Innovations, LLC v. Travel Caddy, Inc., 695 F.3d 1285, 1298 (Fed. Cir. 2012).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 550 U.S. at 418. Rather, it must be shown "by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1068-69 (Fed. Cir. 2012). "In considering motivation . . . , the problem examined is not the specific problem solved by the invention," because "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." Insite Vision Inc. v. Sandoz, Inc., 783 F.3d 853, 859 (Fed. Cir. 2015). Rather, motivation must be viewed from the perspective of the prior art. Id.

"The ultimate judgment of obviousness is a legal determination." KSR, 550 U.S. at 427. The court must make subsidiary factual findings as to: "(1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." In re Cyclobenzaprine Hydrochloride, 676 F.3d at 1068; see also Graham v. John Deere Co., 383 U.S. 1, 17 (1966); KSR, 550 U.S. at 415.

The parties agree that all ingredients in the asserted claims, including enalapril itself, were individually known prior to Azurity's invention, and that it was known that enalapril could be mixed with water to make a liquid dosage form. Azurity also did not seriously challenge Alkem's evidence that it was known that enalapril liquids could include buffers, preservatives, sweeteners,

and flavors—including the same choices for these ingredients as used in the asserted claims. Notably, at the time of the invention at issue, Azurity itself marketed the Epaned Kit, which contained enalapril in the claimed concentration, a citrate buffer, sweeteners, and paraben preservatives. (Kit Label § 11.)

It was, however, also undisputed that the prior art did not disclose any liquid formulation of enalapril known to be stable for a year or more at refrigerated temperature. The parties disagree as to whether a POSA would have expected, before Azurity's invention, that enalapril in water could be as stable as the asserted claims require. The parties also disagree as to whether it would have been obvious to use the particular combination of ingredients recited in the claims.

For the reasons discussed below, I find that Alkem has proven by clear and convincing evidence that the asserted claims would have been obvious to a POSA as of March 18, 2016. Alkem's evidence persuasively established that a POSA would have expected that enalapril could be stable for a year or more in water at refrigerated temperature. I also credit Alkem's interpretation of the prior art that enalapril in water would be most stable if combined with a buffer to keep the pH at "about 3," a range that includes claimed pHs near 3.3. The remaining ingredients—flavors, sweeteners, and preservatives—were known, and the requirements of a manufactured oral liquid would provide a motivation to combine these known ingredients into a single product. The result is Azurity's claimed invention.

1. Expectation of Success in Developing a Long-Term Stable Enalapril Liquid

The heart of the parties' obviousness dispute is whether a POSA would have reasonably expected that enalapril in water could be as stable as the claims require—that is, at least 95% stable at refrigerated temperature after 12, 18, or 24 months. To prove that Azurity's invention

was obvious, Alkem must establish that "a [POSA] would have had a reasonable expectation that" attempting to make a long-term stable enalapril liquid "would succeed." Leo Pharmaceutical Prods. v. REA, 726 F.3d 1346, 1357 (Fed. Cir. 2013). For Alkem to meet this burden, "the expectation of success need only be reasonable, not absolute." Pfizer, Inc. v. Apotex, Inc, 480 F.3d 1348, 1364 (Fed. Cir. 2007). It is not enough for Alkem to show that it would have been "obvious to try" making a long-term stable enalapril liquid, but, at the same time, "absolute predictability of success is not required." Id. at 1365. And the fact that any candidate stable enalapril liquid would require "verifi[cation] through testing" does not necessarily mean that a POSA would not reasonably expect the attempt to succeed. Id. at 1364.

No prior art reference states either that it was or was not possible to make an enalapril liquid that was 95% stable for 12 to 24 months at refrigerated temperature. The longest examples of stability mentioned in the prior art are in: (1) the '747 patent, which states that some liquids are 90% stable for 36 weeks (252 days) at an unspecified temperature; and (2) a prior study mentioned in Allen, which reportedly produced enalapril liquids stable for 262 days (at an unspecified percentage) at room temperature despite using a non-optimal pH. (See '747 patent, col. 13:5-33; Allen at 1917-18.) On the other hand, no prior art reference includes data showing that enalapril in water at refrigerated temperature and a pH near 3 was less than 95% stable for the duration of whatever test was conducted. Thus, prior art publications did not conclusively reveal whether enalapril in water at a pH near 3 could be stable for 12 to 24 months.

Azurity interprets this state of the art as teaching that enalapril was generally unstable in water and that long-term stability was out of reach. Azurity's expert Dr. Little testified that the "breadcrumbs" in the prior art suggesting how to achieve long-term stability were too thin to create a likelihood of success. (N.T. 487-89.) Dr. Little also considered it significant that prior art studies

of enalapril used various pHs, some quite different than Allen's reported most stable pH of 3. (N.T. 488.)

Alkem responds that a POSA would have expected that enalapril could be stable in water. Alkem's counsel acknowledged that the prior art did not provide a "direct road map" for making enalapril stable, but Alkem's expert Dr. Constantinides testified that it would be an "easy task" to make an enalapril liquid stable for 18 or 24 months based on knowledge in the prior art. (N.T. 320 (counsel); N.T. 316, 371 (Constantinides).) Specifically, Dr. Constantinides testified that a POSA would be motivated to optimize the stability of an enalapril liquid to 12, 18, preferably 24 months and would have known how to do so, making such level of stability expected. (N.T. 308, 321-22, 355 (Constantinides).)

The parties agree on the contents of the prior art but disagree as to how a POSA would interpret statements in those publications. First, the parties disagree how a POSA would interpret positive statements expressing that enalapril could be stable in water. For example, Allen shows high stability at a pH of 3.9 over 60 days at refrigerated temperature and concludes that these liquids "were stable" for the duration of the test; Sosnowska shows enalapril liquids with a pH of 3 that are at least 98% stable over 30 days at refrigerated temperature; Nahata shows an enalapril liquid with a pH of 4.7 having 95.8% of the enalapril remaining after 91 days and concludes that "enalapril maleate is stable in widely available vehicles"; Casas shows a graph with no visible change in enalapril concentration at pHs of 2.55 to 2.78 over 50 days refrigerated temperature (although Casas mentions, without data, significant degradation after 90 days); and the specification of the '747 patent states that liquid formulations exist that are 90% stable for 36 weeks (which is 252 days or 69% of a year).

Dr. Constantinides opined that these studies would have given a POSA confidence that

long-term stability was possible. (See N.T. 382-84.) I find his opinion convincing. The stability of enalapril had been investigated numerous times and was always found to be sufficiently stable for the application at hand. And, with the exception of one sentence unaccompanied by data in Casas, no study had shown any substantial degradation of enalapril in water at a pH near 3 and refrigerated temperature. Contrary to Azurity's interpretation, the prior art simply does not convey an impression that enalapril is generally unstable in water.[21]

Azurity advocates that an expectation of success has not been proven on several grounds. First, Azurity notes that Dr. Little testified that extrapolating from prior-art data to the high level of stability required by the claims (95% at 12, 18, or 24 months) was too speculative to give a POSA hope that the high level of stability required by the claims could be achieved. But Dr. Little's opinion placed too much emphasis on studies of enalapril under conditions that were known not to be ideal. Such studies show only that some prior researchers who were not trying to achieve long-term stability made formulations that were not long-term stable, not that long-term stability was difficult to achieve.

For example, prior-art publications that studied the feasibility of compounding used commercially available liquids to evaluate whether an enalapril mixture made from those liquids could

[21] Alkem also asks me to consider the fact that formulators commonly use accelerated stability testing, in which degradation is measured at elevated temperatures. I agree with Alkem that this fact is relevant, but will give it less weight because no expert clarified how far the stability data in the prior art could be extrapolated. Alkem attempted to elicit this testimony from Dr. Constantinides, but it was objected to on the ground that it went outside the scope of his report, and the question was withdrawn. (N.T. 271-76.) I also place little weight on Alkem's reference to the stability of enalapril powders described in the '747 patent because I credit Dr. Little's testimony that enalapril was known to react with water and a POSA would not view the stability of enalapril powder as indicative of its stability in water. Nevertheless, for the reasons stated above, I am ultimately persuaded by Dr. Constantinides's view that the prior art would have conferred an expectation of success that enalapril could be long-term stable in water.

be left on the shelf, unrefrigerated, for short periods of time. (E.g., Casas at 272 (developing an enalapril liquid that "a Pharmacist could easily prepare with available and low cost materials"); Allen at 1918 (using Ora-Sweet and cherry syrup); Sosnowska at 321 (using "commercially available tablets"); Nahata at 1155-56 (using "readily available vehicles"); N.T. 558 (Little) (prior art studies were not trying to achieve long-term stability); N.T. 373-74 (Constantinides) (Nahata was using "commercially available vehicles").) Allen itself makes the point that prior studies that used a pH of 5 rather than 3 may not be indicative of the stability that could be achieved at a pH closer to 3. (Allen at 1918.) I find that a POSA would not be dissuaded by these studies from believing that long-term stability was achievable.

Azurity also points to a sentence in Casas stating that "[a]fter 3 months of study, at the three temperatures studied drug content of [the formulation] decreased by 40%." (Casas at 277.) Azurity notes that although Casas was studying compounded liquids, it included liquids with pHs of 2.78 (which Dr. Constantinides testified was "about 3") that were stored at refrigerated temperatures. I agree with Azurity that Casas could suggest to a POSA that it was possible to make an enalapril liquid that was not stable in water at refrigerated temperature for more than 90 days even if a pH near 3 were used. Dr. Constantinides also acknowledged that the stability data presented in Casas is not predictive of 12 months of stability. (N.T. 347-48.) However, in the context of the other prior art, I conclude that Casas would not dissuade a POSA or teach away from expecting success in making a long-term stable enalapril liquid. Notably, the '747 patent mentions that some liquids created by mixing enalapril in Ora-Sweet SF remain at least 90% stable after 252 days. ('747 patent, cols. 13:5-33.) Thus, a POSA could interpret Casas's mention of 40% degradation after 90 days not as the inevitable result of putting enalapril in water but as only the result of "[that] particular study." (See N.T. 347 (Constantinides).) And, moreover, Casas was not attempting to

achieve long-term stability, Casas's graph contains no data beyond 60 days, and Casas discarded test formulations after 30 days due to microbial contamination. (Casas at 275.)

I also find that Dr. Little's testimony overemphasized the way prior art references defined "stable" rather than the level of stability that was actually achieved. For example, Dr. Little opined that a POSA would not expect that 95% stability was achievable because Sosnowska defined "stable" as at least 90% enalapril remaining, even though the data in Sosnowska showed that the average amount of enalapril remaining at the end of the test period was at least 98%. (N.T. 517-18; Sosnowska at 322.) Similarly, the fact that prior-art researchers collected data for less than a year reflects the requirements of compounding and does not convey the researchers' view that the drug would become unstable after the testing period. (E.g., Nahata at 1157 (concluding that enalapril "is stable" based on short-term studies).)

Throughout trial, Azurity pointed to the 60-day shelf life of its Epaned Kit as evidence that the two-year stability of the present invention was a dramatic improvement. (E.g., N.T. 64-65, 74 (Beckloff).) But the present invention claims stability at refrigerated temperature, not room temperature. No witness testified how long the Kit liquid would be stable if it were kept refrigerated. And Azurity's ready-to-use Epaned product also has a shelf-life of 60 days when not refrigerated, the same as the Kit. (N.T. 74 (Beckloff).) The comparison Azurity attempts to draw between the present invention and the Epaned Kit is therefore uninformative.

Azurity also directs me to FDA guidance stating that a "registration application" submitted to that Agency should contain stability data spanning at least 6, and preferably 12 months. (FDA Guidance §§ 1.1 (scope), 2.2.7.) I do not find the FDA's guidance informative on the question before me. The rigor of testing needed to approve a product is naturally greater than that needed to confer an expectation of success, which "need only be reasonable, not absolute." Pfizer v. Apotex,

480 F.3d at 1364.

For these reasons, I find that Alkem has proven by clear and convincing evidence that the prior art would have led a POSA to expect success in making a long-term stable enalapril liquid. The prior art did not show that enalapril's long-term stability in water was guaranteed, or that it would necessarily be stable for any particular length of time or meet any particular threshold. But the prior art did confer a reasonable expectation that mixing enalapril with water and adjusting the pH to about 3 could result in a drug that was highly stable for a long period of time.

2. Motivation to Make an Enalapril Liquid Long-Term Stable

Alkem must also prove that a POSA would be motivated to make an enalapril liquid as stable as the claims require. Motivation "may be found in many different places and forms." PAR Pharmaceutical, Inc. v. TWI Pharmaceuticals, Inc., 773 F.3d 1186, 1197 (Fed. Cir. 2014). It "does not have to be explicitly stated in the prior art, and can be supported by testimony of an expert witness regarding knowledge of a person of skill in the art at the time of invention." Id.

I conclude that a POSA would know that it was necessary to make an enalapril liquid with long-term stability due to the requirements of distribution time and the FDA's requirements regarding shelf-life. (See, e.g., N.T. 63-64 (Beckloff); N.T. 316 (Constantinides); Sosnowska at 321 ("It is important that the drug should be stable in the vehicle for the proposed duration of storage and administration of the product.").) Dr. Constantinides also credibly testified that a formulator making a ready-to-use liquid would want it to be as stable as the product already on the market—the Kit—which was 24 months. (N.T. 379.) The FDA's guidance provides a motivation to measure stability with a 95% threshold because it defines a "significant change" as, among other things, "[a] 5 percent change in assay from [the drug's] initial value." (FDA Guidance § 2.2.7.1.) Thus, a

POSA would have been motivated to make an enalapril formulation as stable as the claims require.

Azurity posits that once the Epaned Kit became available, there was no longer a motivation to make enalapril stable enough to be used as a ready-to-use liquid. But Alkem does not need to show that a ready-to-use liquid was a better way to make a liquid dosage form of enalapril than the Epaned Kit, just that it was a "suitable" way "from which the prior art did not teach away." PAR Pharmaceutical, 773 F.3d at 1197-98. I find that Alkem has met that burden.

3. Achieving Claimed Stability

Alkem must also show that it would have been obvious to a POSA "how" to make an enalapril liquid as stable as the claims require. See In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) (invention not obvious where prior art did not teach "how to achieve it").

I disagree with Alkem that the stability limitations would have been obvious through the doctrine of "inherency," which renders a claim limitation obvious if it is "the natural result of the combination of elements explicitly disclosed by the prior art." PAR Pharmaceutical, 773 F.3d at 1196. No evidence was offered at trial that the claimed stability was a "property[] inherently possessed" by any formulation made prior to Azurity's invention. Persion Pharmaceuticals LLC v. Alvogen Malta Operations Ltd., 945 F.3d 1184, 1190 (Fed. Cir. 2019). Alkem also failed to establish that stability is "necessarily present" in the combination of claimed ingredients. See In re Kubin, 561 F.3d 1351, 1357 (Fed. Cir. 2009).

But I agree with Alkem that the claimed stability would have been obvious because a POSA would have known how to achieve it through "routine application of a well-known problem-solving strategy." Pfizer v. Apotex, 480 F.3d at 1368 (quotation marks omitted); see also Jerry Harvey 809 F. App'x 919, 922-23 (Fed. Cir. 2020) (finding obviousness where there was a motivation

to achieve the claimed result, an expectation of success in doing so, and capability to achieve it through routine experimentation). A formulator would have been immediately guided to focus on adjusting a single variable, the pH. The prior-art literature strongly conveys that pH drives the stability of enalapril in water and does not suggest that any other variable should be adjusted. (Azurity's contention with respect to mannitol is discussed later.) In view of these teachings, I accept Dr. Constantinides's opinion that this optimization would have been "easy" through "routine experimentation." (N.T. 316, 352; see also N.T. 469 (Little) (noting the ease with which a formulator could make formulations and test them for stability).) The variable was known, the target range (about 3) was known, and the method of adjusting and testing was known. For example, Al-Omari provides a clear template for a POSA to prepare enalapril formulations at a range of pHs within the target range and test the stability of each formulation.

In addition, a formulator would not have needed to wait years for the experimental formulations to degrade; the formulator would have stored the preparations at an elevated temperature and measured the rate of degradation, as in Al-Omari. Azurity criticizes the use of accelerated stability studies, but those criticisms are unavailing. Azurity's first criticism is that accelerated stability results can be misleading because different reactions can occur in the short and long term, such that a solution that appears stable short-term can "fall off a cliff" when tested for longer. But the vague suggestion that short-term stability tests can, in theory, be misleading does not inform whether they would have been misleading for enalapril specifically. Dr. Little did not testify that enalapril degrades differently in the short and long term. Azurity's second criticism is that short-term stability cannot guarantee long-term stability. For example, the FDA does not accept short-term stability tests for use in demonstrating that a formulation is stable for 12 months. But a POSA would not have to conclude that long-term stability was guaranteed to choose a formulation

for long-term testing.

Although Azurity makes a principled argument that optimizing pharmaceutical formulations can sometimes be a daunting task due to the number of variables potentially involved, the facts of this case show that optimizing the stability of enalapril in water is a narrower task that does not involve many variables. "[O]bviousness law . . . recognizes an important distinction between combining known options into a finite number of identified, predictable solutions and merely throwing metaphorical darts at a board in hopes of arriving at a successful result[.]" Leo Pharmaceutical Prods., 726 F.3d at 1357 (citations and quotation marks omitted); see also Adapt Pharma Operations Ltd. v. Teva Pharmaceuticals USA, Inc., 25 F.4th 1354, 1383 (Fed. Cir. 2022) (a " 'general motivation' to experiment" does not make an invention obvious). Thus, "the discovery of an optimum value of a variable in a known process is usually obvious," in contrast to situations "where there are 'numerous parameters' to try." Pfizer v. Apotex, 480 F.3d at 1368. In addition, a narrow range within which to optimize (a pH of about 3) was known. See In re Cohen, 767 F. App'x 985, 988-89 (Fed. Cir. 2019) (finding optimization within a range known in the prior art to be obvious); In re Peterson 315 F.3d 1325, 1329-30 (Fed. Cir. 2003) (selecting within a range known in the prior art usually obvious). Optimizing a known variable within a known range is a more straightforward task than the open-ended problem of finding some combination of ingredients that achieves stability.

Given all of the above, I find that Alkem has proven by clear and convincing evidence that a POSA would have been able to make a liquid formulation that was long-term stable at refrigerated temperature through routine application of the known method of adjusting the formulation and testing for stability.

4. Choosing the Claimed pH

Some of the asserted claims require that the formulation have a pH within a certain range. The narrowest of these limitations requires that the pH be "about 3.3." (E.g., '621 patent, Claim 7.) Alkem therefore must prove that the asserted claims remain obvious when these limitations are included.

A POSA seeking to develop a liquid formulation of enalapril would review published literature and conclude that the pH at which enalapril was most stable in water was about 3. (Mosher 30 (discussing literature review in general); N.T. 202 (Rabinow); N.T. 260 (Constantinides); Allen at 1917-18; Al-Omari at 898; Casas at 272.) Dr. Constantinides's opinion that a POSA would view 3.3 as "about 3" is credible in light of Allen's statement setting the cut-off for stability at about 2 units away from optimal. (See Allen at 1917 ("At a pH >5, the rate of decomposition increases."); id. at 1918 ("Those liquids were buffered to a pH that was 2 units less acidic than the pH at which the drug has maximum stability.").)

Azurity criticizes the reported optimal pH based on the fact that two references reporting it—Allen and Sosnowska—include a citation to the Merck Index, which lacks that information. In context, however, it appears that Allen cites the Merck Index only for the "pK_a value" of enalapril. (See Allen at 1917; Sosnowska at 322; Merck Index at No. 3605.) I conclude that a POSA would not infer from the Merck Index citations that Allen was incorrect about the maximally stable pH.

Azurity also counters that some published studies on enalapril liquids used pHs other than 3. (E.g., Allen at 1918; Nahata at 1156.) However, those sources do not represent the formulations they describe to be ideal, and several studies expressly state that they used readily available liquids rather than liquids optimized for stability. (E.g., Casas at 272 (developing an enalapril liquid that "a Pharmacist could easily prepare with available and low cost materials"); Allen at 1918 (using

Ora-Sweet and cherry syrup); Sosnowska at 321 (using "commercially available tablets"); Nahata at 1155-56 (using "readily available vehicles"); N.T. 559 (Little) ("the prior art do not state that in those publications the goal was to achieve" long-term stability); N.T. 373 (Constantinides) (Nahata was an "academic investigation").) A POSA would not read these publications as suggesting that a pH other than those near 3 should be used.

Alkem does not contend that a formulator in 2016 would have known before trying to choose 3.3 from among the pHs that are about 3, but takes the position that a formulator would have "optimized" the formulation to find the right pH—that is, tried different values until stability was achieved. For the reasons stated previously, a POSA would have expected success in optimizing stability through pH adjustment and would have been able to achieve the claimed stability through "ordinary skill and common sense" rather than "innovation." KSR, 550 U.S. at 402-03. In particular, a POSA would have focused on pH as the variable to adjust and would have known to adjust it within the range of pHs that are about 3, including 3.3. "[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276 (Fed. Cir. 1980).

For these reasons, I find that Alkem has proven by clear and convincing evidence that the pH limitations of the asserted claims would have been obvious in combination with the other limitations.

5. Choosing the Claimed Ingredients

Alkem must also show, by clear and convincing evidence, that the particular formulation Azurity claimed would have been obvious, including the particular combination of all claimed ingredients. This inquiry "requires assessment of the invention as a whole." Princeton Biochem-

icals, Inc. v. Beckman Coulter, Inc., 411 F.3d 1332, 1337 (Fed. Cir. 2005). "This 'as a whole' assessment of the invention requires a showing that an artisan of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the various elements from the prior art and combined them in the claimed manner." Id. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 550 U.S. at 418.

In evaluating whether a POSA would have been motivated to combine ingredients known in the prior art, I find that the process of drug formulation is instructive. The testimony of Dr. Constantinides, which was consistent with that of Dr. Mosher, was that a formulator begins with the product's desired characteristics—its "target product profile"—and proceeds by selecting ingredients to meet that goal. Thus, the process of formulation provides a motivation to combine elements needed to meet the target properties of the drug, such as combining a preservative (needed for a drug stored in a multi-use container) with a sweetener (needed for a drug administered orally to children). This process also provides a motivation to combine these ingredients with the stability and pH limitations, as a liquid containing these ingredients would need to be stable for the reasons stated above and would need to have a pH at which enalapril is stable.

With that background in mind, I note that it was generally known in the prior art that enalapril could be mixed with water, that those liquids should use pH at which enalapril is stable, that a buffer could be used to maintain the pH, and that enalapril liquids should include sweeteners and preservatives necessary for liquids that are stored in a bottle and orally administered to children. (See N.T. 259, 288-89, 303 (Constantinides); Mosher 70.) In addition, the particular choices of buffers, sweeteners, and preserves claimed were individually known and—more impor-

tantly—known to be usable with enalapril. (See, e.g., Kit Label § 11; '747 patent, col. 8.) Several of them are found in Azurity's own Epaned Kit.

Thus, a formulator seeking to make a ready-to-use enalapril liquid would know to mix enalapril with water, include a buffer to keep it at a pH near 3, and add the other ingredients required by the target profile of an oral liquid stored in a bottle, including a sweetener like sucralose and a preservative such as a mixture of parabens. That is, essentially, the entirety of Azurity's invention. While Azurity claims it found a "specific combination of things" that avoids "all of the different reactions that could potentially happen with" enalapril in water, the steps Azurity took to achieve that goal were largely to try the obvious combination of ingredients and realize that they worked.

Azurity disagrees with this characterization of its invention for several reasons. First, Azurity stresses that it would not have been obvious to take a given enalapril liquid described in the prior art and change its characteristics to match the claimed invention—for example, taking the Epaned Kit and removing mannitol. But the testimony at trial was that drug formulators do not work by taking existing formulations and adding or deleting ingredients. Rather, a formulator would work from a target product profile and add those ingredients required to meet it. (See N.T. 258-59 (Constantinides); Mosher 26.) Dr. Mosher specifically testified that a POSA seeking to make an enalapril liquid would not start with the commercially available liquid Ora-Sweet and attempt to reverse engineer it because determining the effect of each of its numerous ingredients would be prohibitively complicated. (Mosher 69.) Thus, the fact that a prior art reference used, for example, a different preservative than the claimed one does not make the claimed preservative nonobvious if it would have been obvious to a POSA to use the claimed preservative to meet the target product profile.

Azurity next argues that its specific choices of claimed ingredients were not obvious, either

individually or in combination. I address those specific ingredients below.

Choice and Concentration of Buffer The choice and concentration of the claimed buffer follow from the known stable pH of enalapril. Relying on de Villiers, a formulator would have selected a buffer made from sodium citrate and citric acid because de Villiers reports that such a buffer can be used at a pH near 3. And de Villiers shows that determining an appropriate buffer concentration for the target pH would have been routine. The need to make the drug stable would have provided a motivation to combine such a buffer with the other claim limitations.

Preservative and sweetener The need to use a preservative and sweetener follow from the drug's target product profile as an oral liquid, which also provides the motivation to combine these ingredients with the other claim limitations. Azurity's choice of preservative (parabens) and sweetener (sucralose) were known and known to work with enalapril. ('747 patent, cols. 5:28-32, 7:51-59, 7:60-8:37, 22:59; Kit Insert § 11; N.T. 301-02 (Constantinides).) To the extent other preservatives and sweeteners were also known to work with enalapril, a claimed design choice need not "be the best option" to be obvious; it only needs to be "a suitable option from which the prior art did not teach away." PAR Pharmaceutical, 773 F.3d at 1197-98.

Azurity argues that Casas would dissuade a formulator from using preservatives—and, in particular, paraben preservatives—because it states that some patients (especially children) are allergic to them. But Casas made that statement in the context of compounded liquids with short shelf lives, and indeed some of Casas's liquids showed "microbial contamination" after just 30 days. (Cases at 275.) By contrast, a drug in a multi-use container needs a preservative. (Mosher 70.) Casas therefore does not teach that preservatives should not be used in a liquid intended for long-term storage. I also note that Azurity does not claim that its invention dealt with the allergy

risks of parabens any differently than the prior art; rather, Azurity used a known ingredient with all its known advantages and disadvantages.

I therefore conclude that Alkem has proven that Azurity's choice of preservative and sweetener, and its decision to include a flavoring agent, would have been obvious in combination with the other claim limitations.

Absence of Mannitol and Silicon Dioxide Claim 18 of the '482 patent requires that the invention not contain mannitol. In addition, all claims of the '621 patent require that the invention not contain unlisted ingredients that "materially affect the basic and novel properties of the invention," which potentially excludes mannitol and silicon dioxide. Azurity argues that a POSA would not think it obvious to make a formulation without mannitol because the '747 patent describes mannitol as a "stabilizing agent." (See N.T. 492-93 (Little).) The '747 patent also includes stability data for three liquids reconstituted from powders—one powder made with mannitol, one made with lactose, and the other made with sucrose—and states that the powder made with mannitol was most stable. ('747 patent, col. 23.)

I find that Azurity's argument is inconsistent with how a POSA would choose ingredients for a ready-to-use enalapril liquid. A formulator would not start with the formulation described in the '747 patent and attempt to modify it to achieve long-term stability. (Mosher 69.) Rather, a formulator would start with a target product profile and add those ingredients required to meet it. I credit Dr. Constantinides's testimony that a formulator working in this way would simply not introduce mannitol because it is rarely used in liquids.

Because I find that a POSA would have no reason to include mannitol in a ready-to-use enalapril liquid, its absence would have been obvious. To the extent the claims of the '621 patent

also exclude silicon dioxide, the same reasoning applies.

6. Secondary Considerations

In determining whether patent claims are obvious, secondary considerations of nonobviousness must be considered. Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1557 (Fed. Cir. 1985). Azurity offers three: (1) unexpected results, (2) failure of others, and (3) long-felt but unresolved need.

Alkem makes a threshold argument that no secondary considerations apply because any such considerations would lack a nexus to the claimed invention. "In order to accord substantial weight to secondary considerations in an obviousness analysis, the evidence of secondary considerations must have a 'nexus' to the claims, i.e., there must be a legally and factually sufficient connection between the evidence and the patented invention." Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1373 (Fed. Cir. 2017) (quotation marks omitted). "The patentee bears the burden of showing that a nexus exists." Id. Alkem argues there is no nexus in this case because Azurity happens to market a commercial enalapril product—Epaned RTU—that does not practice the asserted claims.

I disagree with Alkem's nexus argument. The nexus rule is that the evidence of secondary considerations must relate to the "the patented invention," not necessarily to any particular product. See Fox Factory, 944 F.3d at 1373. Azurity must show a nexus, but it is a nexus between the evidence and the claims, not between the claims and an unrelated commercial product.

With that understanding, I consider Azurity's evidence of secondary considerations.

Unexpected Results "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art,

and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." Bristol-Meyers Squibb Co. v. Teva Pharmaceuticals USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014). "While a 'marked superiority' in an expected property may be enough in some circumstances to render a compound patentable, a 'mere difference in degree' is insufficient." Id.

The parties' experts disagreed as to whether it would have been unexpected as of March 2016 that an enalapril formulation using the claimed ingredients would have been stable, with Dr. Little testifying that the stability was unexpected and Dr. Constantinides testifying that it was not. (N.T. 321-22 (Constantinides); N.T. 534 (Little).) For the reasons discussed previously with respect to expectation of success, it was not unexpected that enalapril would be stable in water at refrigerated temperature for 24 months. (See, e.g., N.T. 321-22 (Constantinides).) Although the exact stability was not known, published studies suggested it was likely enalapril could be stable long-term. This secondary consideration does not apply.[22]

Failure of Others Evidence that others "tried but failed" to make the claimed invention "is particularly probative of obviousness." In re Cyclobenzaprine Hydrochloride, 676 F.3d at 1082. Azurity did not offer evidence that anyone tried and failed to make a liquid form of enalapril that was long-term stable. Some prior art references described enalapril liquids that were not long-term stable, but, for the reasons discussed previously, none of these authors were trying to achieve long-term stability. This secondary consideration therefore does not apply.

[22] Alkem asks me to disregard Azurity's contention of unexpected results because the evidence Azurity used to support this contention before the Patent and Trademark Office (PTO) consisted of formulations that lacked parabens and therefore did not practice the asserted claims. Given my finding that Azurity's invention was not unexpectedly stable, it is unnecessary to reach Alkem's alternative argument. However, I note that while Azurity does have to prove that any unexpected results have a nexus to the asserted claims, Alkem has not pointed to any prohibition on using evidence gleaned from alternative formulations to support that conclusion.

Long-Felt but Unresolved Need "Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." Apple Inc. v. Samsung Electronics Co., 839 F.3d 1034, 1056 (Fed. Cir. 2016).

Whether there was a long-felt but unresolved need is typically assessed as of the filing date. Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc., 566 F.3d 989, 998 (Fed. Cir. 2009). By the filing date here (March 2016), the Epaned Kit was available, and Azurity has not shown that there was a long-felt but unresolved need for an enalapril liquid that was ready-to-use as opposed to a powder kit. The problems Dr. Mahan attempted to identify with the Epaned Kit were speculative, as he could not name a single instance of a pharmacy reconstituting the Kit incorrectly. (N.T. 440-43.) Similarly, Dr. Mahan's comparison of shelf-life between the Epaned Kit and Epaned RTU is uninformative because it compared the Kit's unrefrigerated shelf-life after compounding to the RTU's refrigerated shelf-life from the date of manufacture. (See N.T. 434-36.) For these reasons, I conclude there did not exist a long-felt but unresolved need for Azurity's invention as of its filing date.

Azurity also argues that because enalapril was administered to children using compounding for so many years, this is evidence that a long-term stable formulation was not obvious, even if compounding had ceased by the time the present invention came about. This evidence consists of Dr. Mahan's testimony that compounding was routinely used to administer enalapril to children even though it entailed safety risks. Because the obviousness inquiry must be "expansive and flexible," KSR, 550 U.S. at 415, I have considered this evidence, but I find it less probative of nonobviousness because it predates the Epaned Kit's patent and label. Even if Dr. Mahan's testimony could show that a long-term stable enalapril liquid was nonobvious prior to the release

of the Epaned Kit, his testimony would not rebut evidence that the Epaned Kit made the claimed invention obvious. In particular, Dr. Mahan's testimony does not overcome Dr. Constantinides's detailed explanation showing how the composition and stability information disclosed in the '747 patent made it obvious how to to develop a ready-to-use enalapril liquid. (See N.T. 286-90 (Constantinides).)[23]

7. Determination of Obviousness

For the reasons set out above, and considering that secondary considerations of nonobviousness are only minimally probative, I find that Alkem has proven by clear and convincing evidence that the asserted claims would have been obvious to a POSA as of the filing date.[24]

[23] The need Dr. Mahan identified is also not especially probative of nonobviousness because no testimony was offered tying the lack of a commercially available enalapril liquid to a lack of scientific know-how for making one—as opposed to it being unprofitable, burdened by regulation, not in demand, or difficult to monetize. (Cf. N.T. 559-60; Casas at 272 ("There are many factors that determine the lack of cost-effectiveness of this market of commercial pediatric oral liquid forms.").) Azurity has thus not shown a "nexus" between the long-felt but unresolved need and the claimed invention. Fox Factory, 944 F.3d at 1373.

[24] Alkem further asks me to defer to the patent examiner's initial decision to reject the asserted claims for obviousness before ultimately allowing those claims based on evidence that different formulations—ones not using the claimed preservatives—were unexpectedly stable. Azurity objects because the PTO's reasons for initially denying the asserted claims are not in the record. "The basis (as opposed to the mere existence) of an examiner's initial finding of prima facie obviousness of an issued patent is … at most only one factual consideration that the trial court must consider in context of the totality of the evidence in determining whether the party asserting invalidity has met its statutory burden by clear and convincing evidence." Pfizer v. Apotex, 480 F.3d at 1360. Alkem's post-trial brief identifies the examiner's initial rejection but provides little information about its basis. Because I find that the trial evidence constituted clear and convincing proof of obviousness, I need not consider what additional effect the examiner's initial rejection might have on that conclusion.

IV. WRITTEN DESCRIPTION

A. Facts Relevant to Written Description

The shared specification of the '482 and '621 patents describes enalapril liquid formulations based on their ingredients, pH, stability, and other characteristics. But, although every asserted claim requires that the liquid contain a preservative that is a paraben or mixture of parabens, the patents' shared specification does not contain a complete example of a liquid that uses only parabens as a preservative. (See N.T. 332-32 (Constantinides); N.T. 543 (Little).) Instead, liquids made using paraben preservatives can only be be constructed by combining ingredients from separate places in the specification.

First, the specification describes a formulation with all of the claimed ingredients except for paraben preservatives:

> In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/mL enalapril maleate; (ii) about 0.70 mg/mL of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/mL citric acid and about 0.15 mg/mL sodium citrate dihydrate; (iv) about 1 of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5 ± 3 °C. for at least 12 months.

(Col. 3:39-48.) Second, the specification states that parabens can be used as the preservative, although it does not say which other ingredients these parabens should be combined with. (Col. 6:37-39.) Finally, with regard to the stability limitations, the specification states that "[t]he enalapril oral liquid formulations described herein are stable" under various definitions, some of which closely parallel the claim language and some of which are significantly less stringent (e.g., "for at least 1 month"). (Cols. 18:57-63, 19:15-20.)

Azurity's expert Dr. Little acknowledged that the specification does not contain "a disclosure of a formulation that meets all of the asserted claim limitations" of any asserted claim. (N.T.

543 (Little).) Dr. Little also testified that to find a paraben-containing stable combination from ingredients in the specification, a POSA would "mak[e] … embodiments which are described in the specification and test[] them for stability." (N.T. 469.)

The specification also contains six sections of "examples" of enalapril liquids identified as A, B, C, D, E, and G. ('621 patent, cols. 32-40.) Examples A though E contain data on the stability of those liquids. (See cols. 32-39.) Each example liquid contains at least one preservative that is not a paraben. (Id.; N.T. 332-32 (Constantinides).) Only Examples A and C describe liquids containing parabens, although these liquids also contain other preservatives, as well as other unclaimed ingredients such as mannitol and silicon dioxide. ('621 patent, cols. 32-34; N.T. 331-32 (Constantinides).) The specification contains stability data for these examples, none of which extends beyond 8 weeks of testing, and the specification does not state whether any of the example liquids would be stable for 12, 18, or 24 months.

B. Discussion

A patent must contain a written description that "clearly allow[s] persons of ordinary skill in the art to recognize that the inventor invented what is claimed." Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (alterations and quotation marks omitted). "The essence of the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention." Nuvo Pharmaceuticals (Ireland) Designated Activity Co. v. Dr. Reddy's Labs. Inc., 923 F.3d 1368, 1376 (Fed. Cir. 2019). "Requiring a written description of the invention limits patent protection to those who actually perform the difficult work of 'invention'—that is, conceive of the complete and final invention with all its claimed

limitations—and disclose the fruits of that effort to the public." Id. Therefore, "a description that merely renders the invention obvious does not satisfy the requirement[.]" Ariad Pharmaceuticals, 598 F.3d at 1351. And "[t]eaching how to make and use an invention does not necessarily satisfy the written description requirement." Nuvo Pharmaceuticals, 923 F.3d at 1382.

"[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." Ariad Pharmaceuticals, 598 F.3d at 1352. "[W]ritten description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described; it is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work, which is an enablement issue." Alcon Research Ltd. v. Barr Labs., Inc., 745 F.3d 1180, 1191 (Fed. Cir. 2014). Thus, a lack of empirical data showing that described formulations meet all claim limitations does not mean that the claims lack written description. See id.

The claims at issue in this case use "functional language" to mark the boundaries of the claimed invention. See Ariad Pharmaceuticals, 598 F.3d at 1349. That is, Azurity does not claim ownership of all enalapril liquids made from water, buffers, sweeteners, and parabens—it only claims the subset of those liquids that are stable. The need for written description "is especially acute" when functional language is used. Id. In such a case, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus." Id. The specification can meet this standard by disclosing "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."

Id. at 1350. Alkem argues that the specification here does not meet this standard because a POSA reading the specification would not know which enalapril formulations containing parabens are as stable as the asserted claims require.

For the reasons that follow, I find that all asserted claims lack written description because the specification describes a large variety of ways to combine ingredients but does not say which combinations that use paraben preservatives are stable. That is, if a POSA were to combine ingredients from the specification, they would not know whether they would have the claimed invention.

Initially, Azurity is correct that aspects of the invention described separately in the specification can be combined to meet all limitations of the asserted claims. Those are: (1) ingredients other than parabens that appear in column 3; (2) parabens that appear in column 6; and (3) stability characteristics that are described in column 18. The difficulty is that the specification does not say whether any combination involving parabens meets the stability limitations. The specification lists many buffers, sweeteners, preservatives, and pHs that can be combined, but is largely silent on how these ingredients relate to stability. As Dr. Little acknowledged, a POSA seeking to determine which combinations involving parabens are stable would "mak[e] … embodiments … and test[] them for stability." (N.T. 469 (Little).) Therefore, while a formulation meeting all claim limitations could theoretically be constructed by picking and choosing different parts of the specification, "a POSA is deprived of any meaningful guidance into what [formulations] beyond the examples and formulas, if any, would provide the" claimed stability. Idenix Pharmaceuticals LLC v. Gilead Sciences Inc., 941 F.3d 1149, 1164 (Fed. Cir. 2019). Because "the claimed invention does not appear in the specification," the patents' written description is inadequate. Ariad Pharmaceuticals, 598 F.3d at 1348.

Azurity also takes the position that it would have been simple for a POSA to determine

experimentally which combinations involving parabens are stable. Azurity's position is credible in light of my finding that a stable enalapril liquid with a paraben preservative was obvious even before Azurity's invention. But "a description that merely renders the invention obvious does not satisfy the written description requirement[.]" Ariad Pharmaceuticals, 598 F.3d at 1351. Because "one could not know which, if any, individual [variants] would yield [the claimed stability] without actually making and testing the variants," stable variants containing parabens are not adequately described. Novozymes A/S v. DuPont Nutrition Biosciences APS, 723 F.3d 1336, 1350 (Fed. Cir. 2013). The specification does not need to prove which paraben-containing formulations are stable or provide evidence that they are stable, but it does need to guide a reader to identify formulations meeting all claim limitations. Ariad Pharmaceuticals, 598 F.3d at 1348. The specification here does not provide the required guidance regarding which paraben-containing enalapril formulations are stable.

Azurity also references the stability testing data contained in the specification. But this data also fails to provide guidance as to which paraben-preserved formulations are stable. First, no example is preserved using only parabens: each contains at least one preservative that is not a paraben.[25] (N.T. 331-34 (Constantinides).) Second, the specification draws no conclusion that any tested formulations are stable. While I assume, given Alkem's burden and the lack of contrary evidence, that these short-term stability tests are valid, the specification does not identify any of

[25] Azurity points out that the asserted claims of the '482 patent may be construed to encompass formulations that contain multiple preservatives. But Dr. Little's concession that the specification does not disclose a formulation meeting all claim limitations implies that these examples differ from the claims. (See N.T. 543 (Little).) In any event, if the specification only describes how to make paraben formulations stable by mixing them with other preservatives, it does not describe formulations that (like the accused product in this case) use only paraben preservatives.

these examples as a stable, paraben-preserved liquid.

For the foregoing reasons, I find that Alkem has proven by clear and convincing evidence that the asserted claims are invalid for lack of written description.[26]

V. CONCLUSION

For the reasons set out above, I conclude that Alkem's ANDA infringes all asserted claims. I also find that those claims are invalid for obviousness and lack of written description.

An appropriate order follows.

[26] I do not reach Alkem's alternative argument that the asserted claims lack written description because the specification does not describe formulations using single-paraben preservatives.

US010786482B2

(12) **United States Patent**
Mosher et al.

(10) **Patent No.: US 10,786,482 B2**
(45) **Date of Patent: *Sep. 29, 2020**

(54) **ENALAPRIL FORMULATIONS**

(71) Applicant: **Silvergate Pharmaceuticals, Inc.**, Greenwood Village, CO (US)

(72) Inventors: **Gerold L. Mosher**, Kansas City, MO (US); **David W. Miles**, Kansas City, MO (US)

(73) Assignee: **SILVERGATE PHARMACEUTICALS, INC.**, Greenwood Village, CO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/177,159**

(22) Filed: **Oct. 31, 2018**

(65) **Prior Publication Data**

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(51) **Int. Cl.**

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A61K 9/00	(2006.01)
A61K 47/26	(2006.01)
A61K 47/12	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/401*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/0095*** (2013.01); ***A61K 47/12*** (2013.01); ***A61K 47/26*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/401; A61K 47/12; A61K 47/26; A61K 9/0053; A61K 9/0095
See application file for complete search history.

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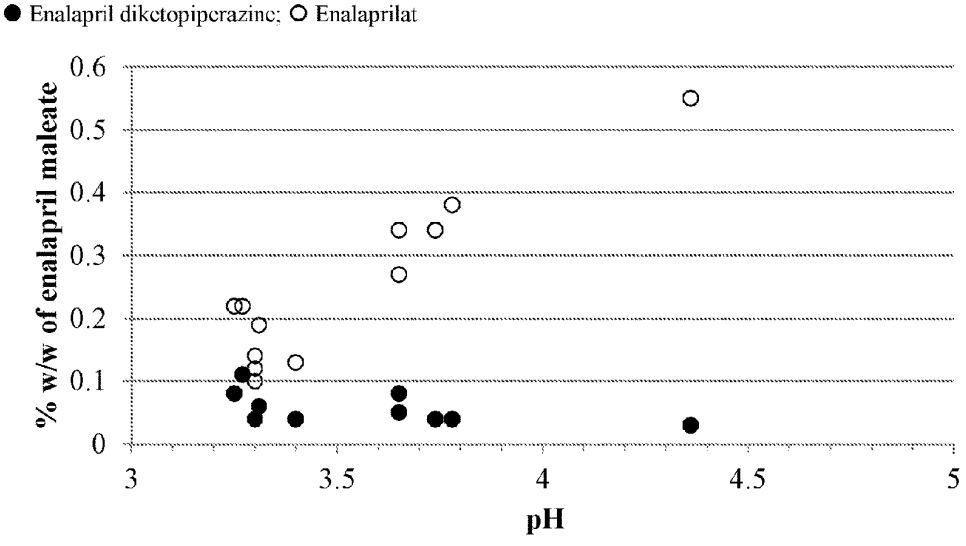
(74) *Attorney, Agent, or Firm* — Wilson, Sonsini, Goodrich & Rosati, P.C.

(57) **ABSTRACT**

Provided herein are stable enalapril oral liquid formulations. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

28 Claims, 2 Drawing Sheets



Dist. Delaware
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SLVGT_RTU_00003996

Related U.S. Application Data

Jun. 5, 2017, now Pat. No. 9,808,442, which is a continuation of application No. 15/081,603, filed on Mar. 25, 2016, now Pat. No. 9,669,008.

(60) Provisional application No. 62/310,198, filed on Mar. 18, 2016.

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FIG. 1

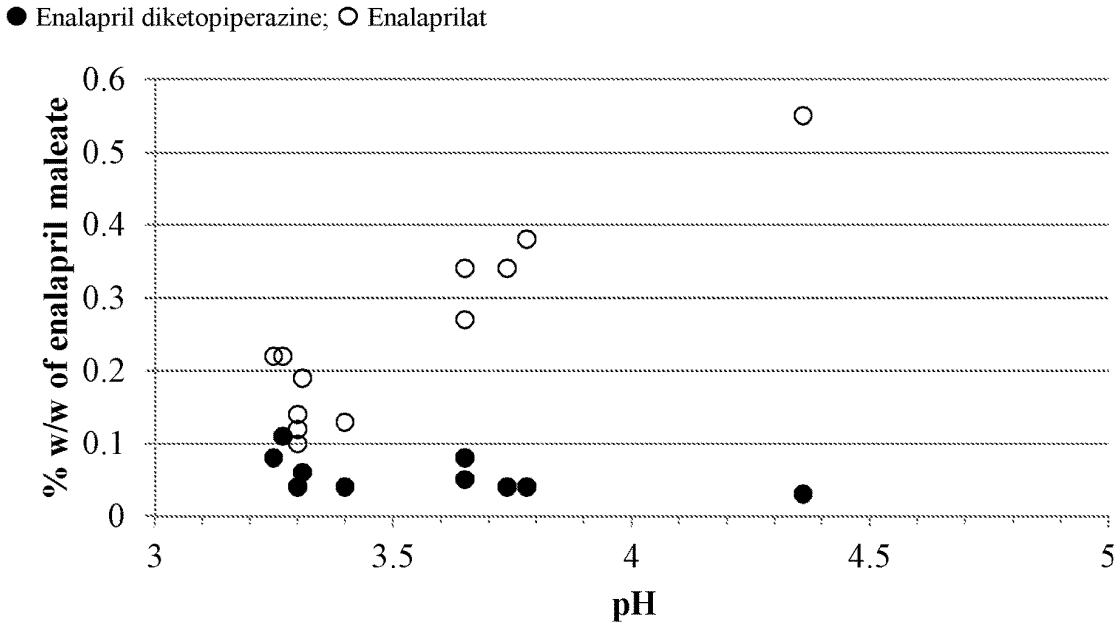
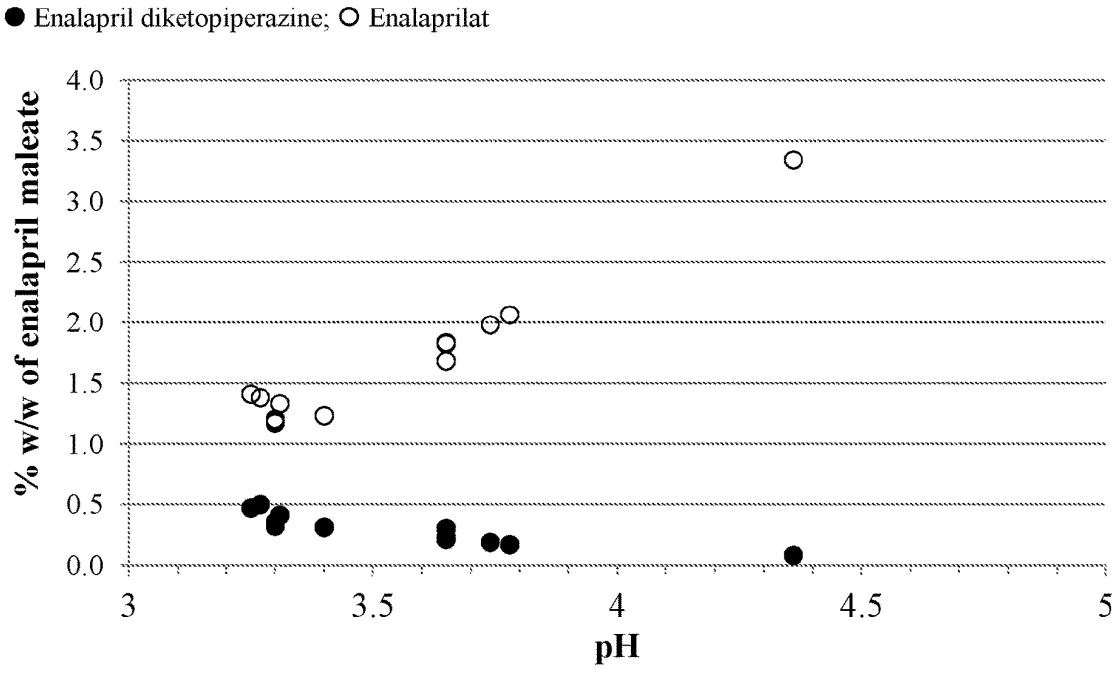

● Enalapril diketopiperazine; ○ Enalaprilat
% w/w of enalapril maleate
0.6
0.5
0.4
0.3
0.2
0.1
0
3
3.5
4
4.5
5
pH

FIG. 2


● Enalapril diketopiperazine; ○ Enalaprilat
% w/w of enalapril maleate
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3
3.5
4
4.5
5
pH

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

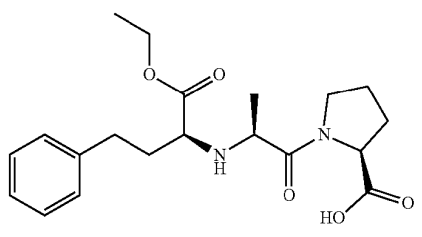
This application is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018, which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

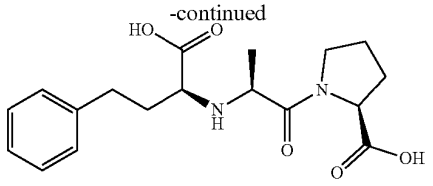
A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers. calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptydyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



Enalapril

-continued



Enalaprilat

Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof (ii) a sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 mg/ml. In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water;

wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w of solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mmm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed descrip-

tion that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. **1**: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. **2**: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rending the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83

mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005-maltodextrin, sorbitol, and fructose combination and Product Code 918.010-water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Viriginia Dare), Maltisweet™ (maltitol solution, Ingredion), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn

syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32

mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2%

w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and Preservative Incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

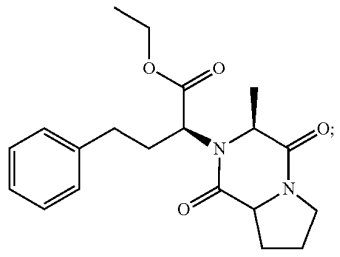
Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

In some embodiments, the oral liquid formulation comprises a buffer.

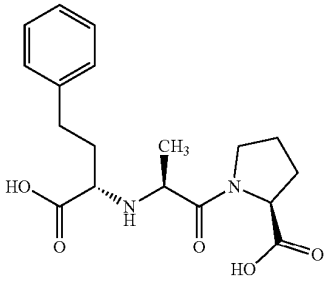
In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



enalapril diketopiperazine



enalaprilat

In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. **1** and FIG. **2**). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodiments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml,

about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34% w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/ml, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the

oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18

months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±3° C. In some embodiments, refrigerated condition is about 2° C., about 2.1° C., about 2.2° C., about 2.3° C., about 2.4° C., about 2.5° C., about 2.6° C., about 2.7° C., about 2.8° C., about 2.9° C., about 3° C., about 3.1° C., about 3.2° C., about 3.3° C., about 3.4° C., about 3.5° C., about 3.6° C., about 3.7° C., about 3.8° C., about 3.9° C., about 4° C., about 4.1° C., about 4.2° C., about 4.3° C., about 4.4° C., about 4.5° C., about 4.6° C., about 4.7° C., about 4.8° C., about 4.9° C., about 5° C., about 5.1° C., about 5.2° C., about 5.3° C., about 5.4° C., about 5.5° C., about 5.6° C., about 5.7° C., about 5.8° C., about 5.9° C., about 6° C., about 6.1° C., about 6.2° C., about 6.3° C., about 6.4° C., about 6.5° C., about 6.6° C., about 6.7° C., about 6.8° C., about 6.9° C., about 7° C., about 7.1° C., about 7.2° C., about 7.3° C., about 7.4° C., about 7.5° C., about 7.6° C., about 7.7° C., about 7.8° C., about 7.9° C., or about 8° C. At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. 25±5° C.; 55±10% RH). In some instances, an accelerated condition is at about 25° C., about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and

the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments. the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*. Nineteeth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*. (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof, and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the

liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2×10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset

of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76, mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet

formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max}, T_{max}, C_{min}, $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propanolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxyben-

zamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., dilitazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term "about" is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or." The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

"Optional" or "optionally" may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term "therapeutic" means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

"Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term "administering", when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. "Administering" a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term "animal" as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms "patient," "subject" and "individual" are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term "pharmaceutical composition" shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a "therapeutically effective amount" or "effective amount" of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or

undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration

	Formulation (mM citrate)					
Component	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

	Formulation					
Hours at 60° C.	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations

	Formulation		
Component	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29

TABLE B-1-continued

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations

	Formulation		
Component	B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

Hours at 60° C.	Formulation B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations

Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		

TABLE C-1-continued

Composition of Enalapril Maleate Formulations

Component	C1	C2	C3	C4	C5
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage ° C.	Weeks	Formulation C1	C2	C3	C4	C5
			Liquid Formulations				
Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		
	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
Enalaprilat	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations

Component	D1	D2	D3	D4	D5	D6
Powder Formulation (grams)						
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
Liquid Formulations (mg/mL)						
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	D1	D2	D3	D4	D5	D6
Liquid Formulations								
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		

TABLE D-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)

Storage		Formulation					
° C.	Weeks	D1	D2	D3	D4	D5	D6
40	0	0.03	0.02	0.03	0.03	0.13	0.14
	4	4.76	4.42	4.76	6.45	5.55	5.24
	8	8.95	8.64	9.61	12.94	12.73	12.18
	12	11.01	10.64	11.41	16.16		
	26	17.18	17.11	18.30	27.36		

Example E: Stability of Solution Formulations of Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)

Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
	19-23	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28
		12	0.58	0.59	0.53	0.51	0.48	0.45
		26	1.10	1.10	1.00	0.95	0.97	0.92
		52					2.30	2.15
		62	3.02	3.04	2.75	2.64		
	40	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76	1.68
		8	4.02	3.99	3.99	3.62	3.37	3.13
		12	6.72	6.42	6.47	6.00	5.53	5.29
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		
	19-23	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.65	0.65	0.68	0.70	0.50	0.46
		8	1.17	1.19	1.20	1.23	1.03	0.95
		12	1.67	1.69	1.72	1.80	1.30	1.21
		26	3.36	3.38	3.42	3.57	3.07	2.90
		52					6.32	5.88
		62	7.99	8.02	8.04	8.57		

TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
Storage		Formulation					
° C.	Weeks	E1	E2	E3	E4	E5	E6
40	0	0.00	0.00	0.01	0.02	0.00	0.00
	4	4.85	4.93	5.19	5.42	3.33	3.25
	8	8.08	8.06	8.56	9.01	6.65	6.35
	12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. **1** (5° C.±3° C.) and FIG. **2** (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category **3** products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results					
	Formulation				
	G1	G2	G3	G4	G5
Formulation (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
AET Results					
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution Vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat Cm were approximately 115% and

109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on ln (C_{max}), was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on ln (AUC_{last}) and ln (AUC_{inf}), was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. An oral liquid formulation, comprising:
(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
(ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
(iii) about 1 mg/ml sodium benzoate; and
(iv) water;
wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about 5±3° C.

2. The oral liquid formulation of claim **1** further comprising a sweetener.

3. The oral liquid formulation of claim **2**, wherein the sweetener is sucralose.

4. The oral liquid formulation of claim **1** further comprising a flavoring agent.

5. The oral liquid formulation of claim **1**, wherein the formulation does not contain mannitol.

6. The oral liquid formulation of claim **1**, wherein the formulation does not contain silicon dioxide.

7. The oral liquid formulation of claim **1**, wherein the buffer comprises about 0.8 to about 3.5 mg/ml citric acid.

8. The oral liquid formulation of claim **1**, wherein the buffer comprises about 0.1 to about 0.8 mg/ml sodium citrate.

9. The oral liquid formulation of claim **1**, wherein the pH of the oral liquid formulation is less than about 3.5.

10. The oral liquid formulation of claim **1**, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.

11. The oral liquid formulation of claim **1**, wherein the pH of the oral liquid formulation is about 3.3.

12. The oral liquid formulation of claim **1**, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about 5±3° C.

13. An oral liquid formulation, consisting essentially of:
(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
(ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
(iii) about 1 mg/ml sodium benzoate;
(iv) water; and
(v) optionally a sweetener, a flavoring agent, or both;
wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about 5±3° C.

14. An oral liquid formulation, comprising:
(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
(ii) a buffer comprising a mixture of citric acid and sodium citrate, wherein the buffer is present at a concentration between about 5 mM and about 20 mM in the oral liquid formulation;
(iii) about 1 mg/ml of a preservative, wherein the preservative is a paraben or a mixture of parabens; and
(iv) water;
wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 12 months at about 5±3° C.

15. The oral liquid formulation of claim **14** further comprising a sweetener.

16. The oral liquid formulation of claim **15**, wherein the sweetener is sucralose.

17. The oral liquid formulation of claim **14** further comprising a flavoring agent.

18. The oral liquid formulation of claim **14**, wherein the formulation does not contain mannitol.

19. The oral liquid formulation of claim **14**, wherein the formulation does not contain silicon dioxide.

20. The oral liquid formulation of claim **14**, wherein the pH of the oral liquid formulation is less than about 3.5.

21. The oral liquid formulation of claim **14**, wherein the pH of the oral liquid formulation is between about 3 and about 3.5.

22. The oral liquid formulation of claim **14**, wherein the pH of the oral liquid formulation is about 3.3.

23. The oral liquid formulation of claim **14**, wherein the formulation maintains about 95% w/w or greater of the initial enalapril amount at the end of a storage period of at least 18 months at about 5±3° C.

24. The oral liquid formulation of claim **1**, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.

25. The oral liquid formulation of claim **1**, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

26. The oral liquid formulation of claim **1**, wherein the buffer is present at a concentration of about 10 mM in the oral liquid formulation.

27. The oral liquid formulation of claim **14**, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate, and wherein the enalapril maleate is present in the oral liquid formulation at about 1.0 mg/ml.

28. The oral liquid formulation of claim **14**, wherein the buffer is present at a concentration between about 10 mM and about 20 mM in the oral liquid formulation.

* * * * *

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(12) **United States Patent**
Mosher et al.

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(45) **Date of Patent: *Feb. 16, 2021**

(54) **ENALAPRIL FORMULATIONS**

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A61K 47/26	(2006.01)
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(58) **Field of Classification Search**

CPC A61K 31/401; A61K 47/12; A61K 47/26; A61K 9/0053; A61K 9/0095

See application file for complete search history.

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(57) **ABSTRACT**

Provided herein are stable enalapril oral liquid formulations. Also provided herein are methods of using enalapril oral liquid formulations for the treatment of certain diseases including hypertension, heart failure and asymptomatic left ventricular dysfunction.

30 Claims, 2 Drawing Sheets

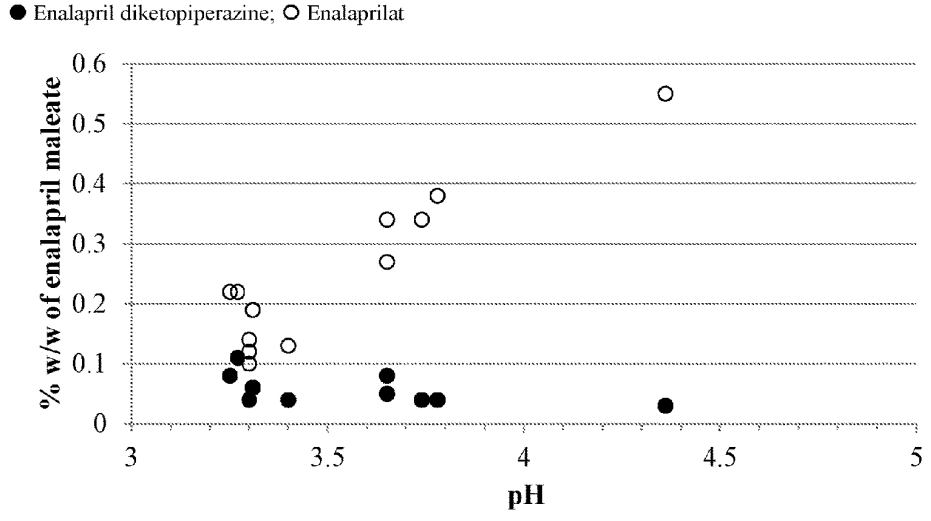

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FIG. 1

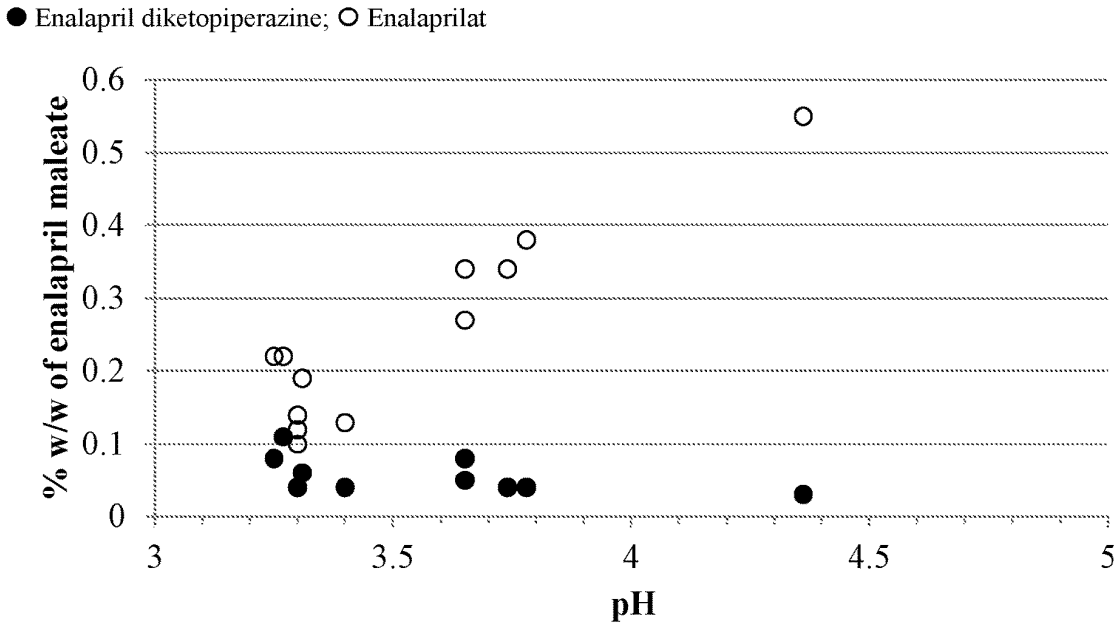
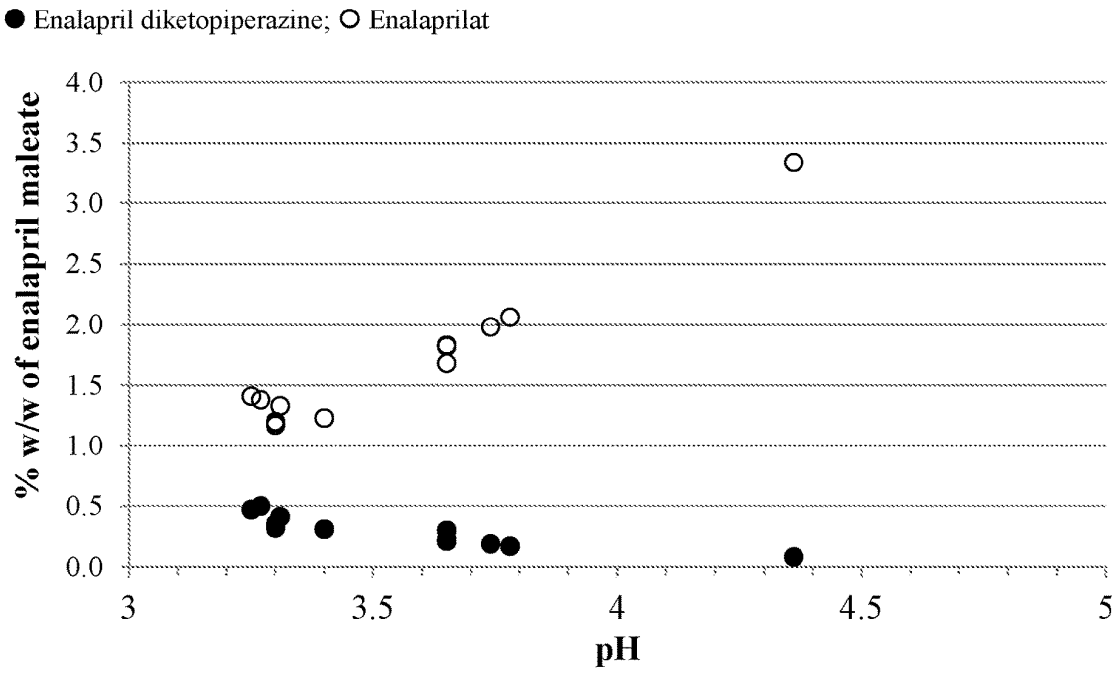

● Enalapril diketopiperazine; ○ Enalaprilat
% w/w of enalapril maleate
0.6
0.5
0.4
0.3
0.2
0.1
0
3
3.5
4
4.5
5
pH

FIG. 2


● Enalapril diketopiperazine; ○ Enalaprilat
% w/w of enalapril maleate
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3
3.5
4
4.5
5
pH

ENALAPRIL FORMULATIONS

CROSS-REFERENCE OF RELATED APPLICATIONS

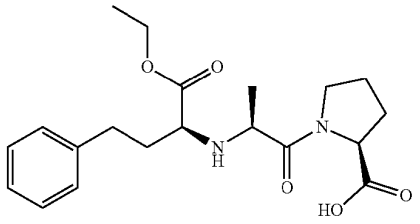
This application is a continuation of U.S. patent application Ser. No. 16/883,553, filed May 26, 2020 which is a continuation of U.S. patent application Ser. No. 16/242,898, filed Jan. 8, 2019, which is a continuation of Ser. No. 16/177,159, filed Oct. 31, 2018, which is a continuation of U.S. patent application Ser. No. 16/003,994, filed Jun. 8, 2018 (now U.S. Pat. No. 10,154,987, issued Dec. 18, 2018), which is a continuation of U.S. patent application Ser. No. 15/802,341, filed Nov. 2, 2017 (now U.S. Pat. No. 10,039,745, issued Aug. 7, 2018), which is a continuation of U.S. patent application Ser. No. 15/613,622, filed Jun. 5, 2017 (now U.S. Pat. No. 9,808,442, issued Nov. 7, 2017), which is a continuation of U.S. patent application Ser. No. 15/081,603, filed Mar. 25, 2016 (now U.S. Pat. No. 9,669,008, issued Jun. 6, 2017), which claims the benefit of U.S. Provisional Patent Application No. 62/310,198, filed Mar. 18, 2016, all of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

Hypertension, or high blood pressure, is a serious health issue in many countries. According to the National Heart Blood and Lung Institute, it is thought that about 1 in 3 adults in the United States alone have hypertension. Left unchecked, hypertension is considered a substantial risk factor for cardiovascular and other diseases including coronary heart disease, myocardial infarction, congestive heart failure, stroke and kidney failure. Hypertension is classified as primary (essential) hypertension or secondary hypertension. Primary hypertension has no known cause and may be related to a number of environmental, lifestyle and genetic factors such as stress, obesity, smoking, inactivity and sodium intake. Secondary hypertension can be caused by drug or surgical interventions, or by abnormalities in the renal, cardiovascular or endocrine system.

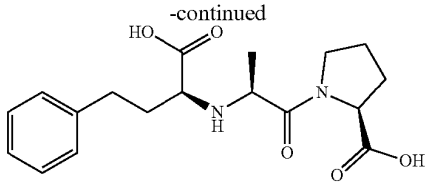
A number of antihypertensive drugs are available for treating hypertension. Various therapeutic classes of antihypertensive drugs include alpha-adrenergic blockers, beta-adrenergic blockers, calcium-channel blockers, hypotensives, mineralcorticoid antagonists, central alpha-agonists, diuretics and rennin-angiotensin-aldosterone inhibitors which include angiotensin II receptor antagonists (ARB) and angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme (ACE) inhibitors inhibit angiotensin-converting enzyme (ACE), a peptydyl dipeptidase that catalyzes angiotension I to angiotension II, a potent vasoconstrictor involved in regulating blood pressure.

Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor of medications. It is rapidly hydrolyzed in the liver to enalaprilat following oral administration. Enalaprilat acts as a potent inhibitor of ACE. The structural formulae of enalapril and enalaprilat are as follows:



Enalapril

-continued



Enalaprilat

Enalapril is currently administered in the form of oral tablets, (e.g., Vasotec®) or in the form of liquid formulations obtained by reconstitution of enalapril powder formulations. In addition to the treatment of hypertension, enalapril tablets have been used for symptomatic congestive heart failure, and asymptomatic left ventricular dysfunction.

SUMMARY OF THE INVENTION

Provided herein are enalapril oral liquid formulations. In one aspect, the enalapril oral liquid formulation, comprises (i) enalapril or a pharmaceutically acceptable salt or solvate thereof; (ii) sweetener that is sucralose (iii) a buffer comprising citric acid; (iv) a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the enalapril is enalapril maleate. In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer in the formulation further comprises sodium citrate dihydrate. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 0.6 to about 1.2 mg/ml. In some embodiments, the amount of sucralose is about 0.5 to about 0.9 mg/ml. In some embodiments, the amount of citric acid in the buffer is about 0.8 to about 3.5 mg/ml. In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 0.1 to about 0.80 In some embodiments, the amount of the sodium benzoate is about 0.2 to about 1.2 mg/ml. In some embodiments, the amount of enalapril or a pharmaceutically acceptable salt or solvate thereof is about 10 to about 25% (w/w of solids). In some embodiments, the amount of sucralose is about 8 to about 18% (w/w of solids). In some embodiments, the amount of citric acid in the buffer is about 17 to about 47% (w/w of solids). In some embodiments, the amount of sodium citrate dihydrate in the buffer is about 1 to about 11% (w/w of solids). In some embodiments, the amount of sodium benzoate is about 12 to about 25% (w/w of solids). In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation, comprises (i) about 1 enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the

formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 0.15 mg/mL sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the pH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation comprises (i) about 19.3% (w/w of solids) enalapril maleate; (ii) about 13.5% (w/w of solids) of a sweetener that is sucralose; (iii) a buffer comprising about 35.2% (w/w of solids) citric acid; (iv) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

In some embodiments, the formulation further comprises a flavoring agent. In some embodiments, the buffer further comprises about 2.9% (w/w solids) sodium citrate dihydrate. In some embodiments, the pH of the formulation is between about 3 and about 3.5. In some embodiments, the PH of the formulation is about 3.3. In some embodiments, the citrate concentration in the buffer is about 5 mM to about 20 mM. In some embodiments, the citrate concentration in the buffer is about 10 mM. In some embodiments, the formulation is stable at about 5±3° C. for at least 18 months. In some embodiments, the formulation is stable at about 5±3° C. for at least 24 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In one aspect, the enalapril oral liquid formulation consists essentially of (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 of a preservative that is sodium benzoate; (v) a flavoring agent; and (vi) water; wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid; and wherein the formulation is stable at about 5±3° C. for at least 12 months.

Also provided herein are methods of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the hypertension is primary (essential) hypertension. In some embodiments, the hypertension is secondary hypertension. In some embodiments, the subject has blood pressure values greater than or equal to 140/90 mm Hg. In some embodiments, the subject is an adult. In some embodiments, the subject is elderly. In some embodiments, the subject is a child. In some embodiments, the formulation is administered to the subject in a fasted state. In some embodiments, the formulation is administered to the subject in a fed state. In some embodiments, the formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

Also provided herein are methods of treating prehypertension in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

In some embodiments, the subject has blood pressure values of about 120-139/80-89 mm Hg.

Also provided herein are methods of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

Also provided herein are methods of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of enalapril oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.7 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5; and wherein the formulation is stable at about 5±3° C. for at least 12 months. In some embodiments, the formulation does not contain mannitol. In some embodiments, the formulation does not contain silicon dioxide.

INCORPORATION BY REFERENCE

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed descrip-

tion that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. **1**: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at 5° C.

FIG. **2**: Effect of pH on degradant formation after 8 weeks of storage of various enalapril solution formulations at room temperature (19-22° C.).

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are stable enalapril oral liquid formulations. Also provided herein are stable enalapril powder formulations for reconstitution for oral liquid administration. These enalapril formulations described herein are useful for the treatment of hypertension, prehypertension, heart failure as well as ventricular dysfunction. The formulations are advantageous over conventional solid dosage administration of enalapril ranging from ease of administration, accuracy of dosing, accessibility to additional patient populations such as to children and the elderly, and an increased patient compliance to medication.

It is generally known that certain segments of the population have difficulty ingesting and swallowing solid oral dosage forms such as tablets and capsules. As many as a quarter of the total population has this difficulty. Often, this leads to non-compliance with the recommended medical therapy with the solid dosage forms, thereby resulting in rending the therapy ineffective. Further, solid dosage forms are not recommended for children or elderly due to increased risk in choking.

Furthermore, the dose of enalapril to be given to children is calculated according to the child's weight. When the calculated dose is something other than the amount present in one or more intact solid dosage forms, the solid dosage form must be divided to provide the correct dose. This leads to inaccurate dosing when solid dosages forms, such as tablets, are compounded to prepare other formulations for children.

For enalapril, one solution to overcoming the use of the tablet form is for a compounding pharmacist to pulverize and crush the enalapril tablet(s) into a powder via mortar and pestle and reconstitute the powder in some liquid form. However forming a enalapril oral liquid in this fashion has significant drawbacks including large variability in the actual dosage, incomplete solubilizing of the enalapril tablet in the liquid, rapid instability, inconsistent formulation methods per compounding pharmacy, and a number of other potential issues. The crushed tablet liquid formulation may also be potentially unsafe due to contamination with residual drugs and other substances from the mortar and pestle or other crushing agent.

Alternatively, enalapril is formulated as enalapril powder compositions for reconstitution as oral liquids as described in U.S. Pat. No. 8,568,747. The powder compositions as described in this patent require mannitol and colloidal silicon dioxide for stability and dissolution. While these powder compositions are an improvement over crushing tablets, they still require a step of mixing with a diluent. The stable enalapril oral liquid formulations described herein require no extra steps or manipulation prior to administration to a subject. Further, the stable enalapril oral liquid formulations described herein do not require or need mannitol or colloidal silicon dioxide for stability and dissolution.

The present embodiments described herein provide a safe and effective oral administration of enalapril for the treatment of hypertension and other disorders. In particular, the embodiments provide stable enalapril oral liquid formulations as well as alternatively enalapril powder formulations for oral liquid administration.

As used herein, "enalapril" refers to enalapril base, its salt, or solvate or derivative or isomer or polymorph thereof. Suitable compounds include the free base, the organic and inorganic salts, isomers, isomer salts, solvates, polymorphs, complexes etc. U.S. Pat. Nos. 4,374,829; 4,472,380 and 4,510,083 disclose exemplary methods in the preparation of enalapril. In some embodiments, the enalapril used in the formulations described herein is an enalapril salt. In some instances, the enalapril salt is enalapril maleate. In other instances, the enalapril salt is in the form of enalapril sodium.

Other ACE inhibitors are contemplated in the formulations within and include but are not limited to quinapril, indolapril, ramipril, perindopril, lisinopril, benazepril, imidapril, zofenopril, trandolapril, fosinopril, captopril, and their salts, solvates, derivatives, polymorphs, or complexes, thereof.

Enalapril Oral Liquid Formulations

Oral liquids include, but are not limited to, solutions (both aqueous and nonaqueous), suspensions, emulsions, syrups, slurries, juices, elixirs, dispersions, and the like. It is envisioned that solution/suspensions are also included where certain components described herein are in a solution while other components are in a suspension.

In one aspect, the enalapril liquid formulations described herein comprise enalapril, a preservative, a sweetening agent, a buffer, and water. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetening agent is xylitol. In one embodiment, the sweetening agent is not mannitol. In another embodiment, the preservative is sodium benzoate. In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In yet another embodiment, the buffer comprises citric acid. In some embodiments, the buffer further comprises sodium citrate. In one aspect, the enalapril liquid formulation described herein comprises enalapril, sucralose, sodium benzoate, citric acid, sodium citrate, and water. In some embodiments, the enalapril liquid formulation herein further comprises a flavoring agent. In some embodiments, the enalapril liquid formulation is not obtained from crushing enalapril tablet and dissolving the powder in a suitable vehicle for oral administration. In some embodiments, the enalapril liquid formulation does not contain silicon dioxide. In some embodiments, the enalapril liquid formulation does not contain mannitol. In some embodiments, the enalapril liquid formulation does not contain lactose. In some embodiments, the enalapril liquid formulation does not contain magnesium stearate. In some embodiments, the enalapril liquid formulation does not contain sodium bicarbonate. In some embodiments, the enalapril liquid formulation does not contain iron oxides.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77

mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, enalapril is present in about 0.76 mg/ml in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 1 mg/ml in the oral liquid formulation. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in molar concentration equivalent to 1 mg/mL enalapril maleate. In some embodiments, the formulation contains enalapril or another pharmaceutically acceptable salt of enalapril in a molar concentration equivalent to 0.76 mg/mL enalapril.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 15% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 18.2% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the solids in the oral liquid formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.4% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.5% w/w of the solids in the oral liquid formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the solids in the oral liquid formulation.

Sweetener in the Enalapril Oral Liquid Formulations

Sweeteners or sweetening agents include any compounds that provide a sweet taste. This includes natural and synthetic sugars, natural and artificial sweeteners, natural extracts and any material that initiates a sweet sensation in a subject. In some embodiments, a solid/powder sweetener is used in the oral liquid formulation described herein. In other embodiments, a liquid sweetener is used in the oral liquid formulation described herein.

Sugars illustratively include glucose, fructose, sucrose, xylitol, tagatose, sucralose, maltitol, isomaltulose, Isomalt™ (hydrogenated isomaltulose), lactitol, sorbitol, erythritol, trehalose, maltodextrin, polydextrose, and the like. Other sweeteners illustratively include glycerin, inulin, erythritol, maltol, acesulfame and salts thereof, e.g., acesulfame potassium, alitame, aspartame, neotame, sodium cyclamate, saccharin and salts thereof, e.g., saccharin sodium or saccharin calcium, neohesperidin dihydrochalcone, stevioside, thaumatin, and the like. Sweeteners can be used in the form of crude or refined products such as hydrogenated starch hydrolysates, maltitol syrup, high fructose corn syrup, etc., and as branded products, e.g., Sweet Am™ liquid (Product Code 918.003—-propylene glycol, ethyl alcohol, and proprietary artificial flavor combination, Flavors of North America) and Sweet Am™ powder (Product Code 918.005—maltodextrin, sorbitol, and fructose combination and Product Code 918.010—water, propylene glycol, sorbitol, fructose, and proprietary natural and artificial flavor

combination, Flavors of North America), ProSweet™ (1-10% proprietary plant/vegetable extract and 90-99% dextrose combination, Viriginia Dare), Maltisweet™ (maltitol solution, Ingredion), Sorbo™ (sorbitol and sorbitol/xylitol solution, SPI Polyols), Invertose™ (high fructose corn syrup, Ingredion), Rebalance M60 and X60 (sucralose and maltodextrin, Tate and Lyle), and Ora-Sweet® sugar-free flavored syrup (Paddock Laboratories, Inc.). Sweeteners can be used singly or in combinations of two or more. Suitable concentrations of different sweeteners can be selected based on published information, manufacturers' data sheets and by routine testing.

In some embodiments, the enalapril oral liquid formulation described herein comprises a sweetening agent. In some embodiments, the sweetening agent is sucralose. In some embodiments, the sweetening agent is xylitol. In some embodiments, the sweetener is not mannitol.

In some embodiments, the enalapril oral liquid formulation described herein comprises sucralose. In some embodiments, sucralose is present in about 0.5 to about 0.9 mg/ml in the oral liquid formulation. In other embodiments, sucralose is present in about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.60 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.70 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.80 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, or about 0.90 mg/ml in the oral liquid formulation. In some embodiments, sucralose is present in about 0.7 mg/ml in the oral liquid formulation.

In some embodiments, sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 8% w/w to about 18% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 9.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sucralose is present in about 16.5% w/w of the solids in the oral liquid formulation.

In some embodiments, the enalapril oral liquid formulation described herein comprises xylitol. In some embodiments, xylitol is present in about 140 mg/ml to about 210 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 140 mg/ml, about 145 mg/ml, about 150 mg/ml, about 155 mg/ml, about 160 mg/ml, about 165 mg/ml, about 170 mg/ml, about 175 mg/ml, about 180 mg/ml, about 185 mg/ml, about 190 mg/ml, about 195 mg/ml, about 200 mg/ml, about 205 mg/ml, or about 210 mg/ml of the oral liquid formulation. In some embodiments, xylitol is present in about 150 mg/ml in the oral liquid formulation. In some embodiments, xylitol is present in about 200 mg/ml in the oral liquid formulation.

In some embodiments, xylitol is present in about 80% w/w to about 99% w/w of the solids in the oral liquid formulation. In other embodiments, xylitol is present in about 80% w/w, about 81% w/w, about 82% w/w, about 83% w/w, about 84% w/w, about 85% w/w, about 86% w/w, about 87% w/w, about 88% w/w, about 89% w/w, about 90% w/w, about 91% w/w, about 92% w/w, about 93% w/w, about 94% w/w, about 95% w/w, about 96% w/w, about 97% w/w, about 98% w/w, or about 99% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w to about 98% w/w of the solids in the oral liquid formulation. In some embodiments, xylitol is present in about 96% w/w of the solids in the oral liquid formulation.

Preservative in the Enalapril Oral Liquid Formulations

Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, EDTA and its salts, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (such as methylparaben, ethylparaben, propylparaben, butylparaben and their salts), benzoic acid, sodium benzoate, potassium sorbate, vanillin, and the like.

In some embodiments, the enalapril oral liquid formulation described herein comprises a preservative.

In some embodiments, the preservative is a paraben and the sweetener is not a sugar (such as, but not limited to glucose, fructose, sucrose, lactose, maltose) or a sugar alcohol (such as, but not limited to xylitol, mannitol, lactitol, maltitol, sorbitol).

In some embodiments, the preservative is sodium benzoate.

In some embodiments, modulation of the pH is desired to provide the best antimicrobial activity of the preservative, sodium benzoate. In some embodiments, the antimicrobial activity of sodium benzoate drops when the pH is increased above 5.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about

3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, sodium benzoate is present in about 0.2 to about 1.2 mg/ml in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml, about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/ml, about 0.91 mg/ml, about 0.92 mg/ml, about 0.93 mg/ml, about 0.94 mg/ml, about 0.95 mg/ml, about 0.96 mg/ml, about 0.97 mg/ml, about 0.98 mg/ml, about 0.99 mg/ml, about 1 mg/ml, about 1.01 mg/ml, about 1.02, mg/ml, about 1.03 mg/ml, about 1.04 mg/ml, about 1.05 mg/ml, about 1.06 mg/ml, about 1.07 mg/ml, about 1.08 mg/ml, about 1.09 mg/ml, about 1.1 mg/ml, about 1.11 mg/ml, about 1.12, mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, or about 1.2 mg/ml in the liquid oral formulation. In some embodiments, sodium benzoate is present in about 1 mg/ml in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.1% w/w, about 15.2% w/w, about 15.3% w/w, about 15.4% w/w, about 15.5% w/w, about 15.6% w/w, about 15.7% w/w, about 15.8% w/w, about 15.9% w/w, about 16% w/w, about 16.1% w/w, about 16.2% w/w, about 16.3% w/w, about 16.4% w/w, about 16.5% w/w, about 16.6% w/w, about 16.7% w/w, about 16.8% w/w, about 16.9% w/w, about 17% w/w, about 17.1% w/w, about 17.2% w/w, about 17.3% w/w, about 17.4% w/w, about 17.5% w/w, about 17.6% w/w, about 17.7% w/w, about 17.8% w/w, about 17.9% w/w, about 18% w/w, about 18.1% w/w, about 18.2% w/w, about 18.3% w/w, about 18.4% w/w, about 18.5% w/w, about 18.6% w/w, about 18.7% w/w, about 18.8% w/w, about 18.9% w/w, about 19% w/w, about 19.1% w/w, about 19.2% w/w, about 19.3% w/w, about 19.4% w/w, about 19.5% w/w, about 19.6% w/w, about 19.7% w/w, about 19.8% w/w, about 19.9% w/w, about 20% w/w, about 20.1% w/w, about 20.2% w/w, about 20.3% w/w, about 20.4% w/w, about 20.5% w/w, about 20.6% w/w, about 20.7% w/w, about 20.8% w/w, about 20.9% w/w, about 21% w/w, about 21.1% w/w, about 21.2% w/w, about 21.3% w/w, about 21.4% w/w, about 21.5% w/w, about 21.6% w/w, about 21.7% w/w, about 21.8% w/w, about 21.9% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about 25% w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 10% w/w to about 25% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 13.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 19.3% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 23.5% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in about 0.1% w/w to about 1% w/w of the solids in the oral liquid formulation. In other embodiments, sodium benzoate is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.4% w/w to about 0.7% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.45% w/w of the solids in the oral liquid formulation. In some embodiments, sodium benzoate is present in about 0.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium benzoate is present in an amount sufficient to provide antimicrobial effectiveness to the enalapril oral liquid formulation described herein. (See Table G-1).

In some embodiments, the preservative is a paraben. In some embodiments, the preservative is a mixture of parabens. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, or about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, or about 2 mg/ml in the liquid oral formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 1.6 mg/ml to about 1.8 mg/ml in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 30% w/w of the solids in the oral liquid formulation. In other embodiments, the paraben or mixture of parabens is present in about 2% w/w,

about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, or about 30% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 2% w/w to about 3% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 23% w/w to about 26% w/w of the solids in the oral liquid formulation. In some embodiments, the paraben or mixture of parabens is present in about 26% w/w to about 30% w/w of the solids in the oral liquid formulation.

Sweetener and preservative incompatibility

Paraben preservatives (especially methylparaben) can react with selected sugars (glucose, fructose, sucrose, lactose, maltose) and sugar alcohols (xylitol, mannitol, lactitol, maltitol, sorbitol) to form transesterification reaction products. This can be undesirable from a formulation and stability standpoint as the transesterification creates additional degradants.

In some embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative. In further embodiments, the enalapril oral liquid formulation described herein does not comprise a paraben preservative when the formulation also comprises a sugar or sugar alcohol.

pH of Enalapril Oral Liquid Formulations

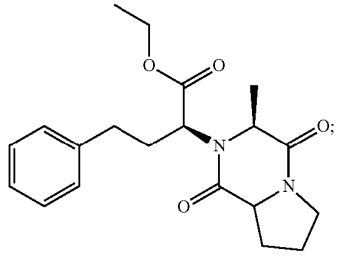
Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co-precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate. calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution. In some embodiments, the buffering agent is not sodium bicarbonate.

In some embodiments, the oral liquid formulation comprises a buffer.

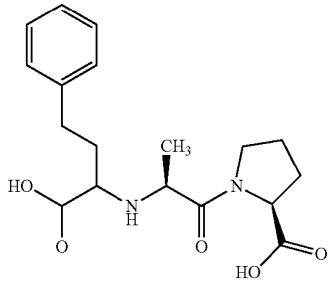
In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises citric acid and sodium citrate dihydrate or an equivalent molar amount of sodium citrate anhydrous. In some embodiments, the sodium citrate is monosodium citrate. In some embodiments, the sodium citrate is disodium citrate. In some embodiments, the sodium citrate is trisodium citrate.

In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises phosphoric acid. In some embodiments, the buffer in the enalapril oral liquid formulation described herein comprises sodium phosphate.

In some embodiments, modulation of the pH is desired to provide a lowered impurity profile. In the exemplary stability studies, the main enalapril degradants are enalapril diketopiperazine and enalaprilat:



enalapril diketopiperazine



enalaprilat

In some embodiments, the percentage of enalaprilat formation is increased when the pH is above 3.5. (See table C-2 and FIG. **1** and FIG. **2**). In some embodiments, the percentage of enalapril diketopiperazine formation is slightly increased as the pH is below 4.

In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is less than about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is between about 3 and about 3.5. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4. In some embodiments, the pH of the enalapril oral liquid formulation described herein is about 3.3.

In some embodiments, the formation of degradants is dependent on the buffer concentration. In some embodiments, the buffer concentration impacts the taste of the enalapril oral liquid formulation.

In some embodiments, the buffer concentration is between about 5 mM and about 20 mM. In some embodi-

ments, the buffer concentration is about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In some embodiments, the buffer concentration is about 5 mM. In some embodiments, the buffer concentration is about 10 mM. In some embodiments, the buffer concentration is about 20 mM.

In some embodiments, citric acid is present in about 0.7 to about 2 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, about 0.8 mg/ml, about 0.81 mg/ml, about 0.82 mg/ml, about 0.83 mg/ml, about 0.84 mg/ml, about 0.85 mg/ml, about 0.86 mg/ml, about 0.87 mg/ml, about 0.88 mg/ml, about 0.89 mg/ml, about 0.9 mg/mL, about 0.91 mg/mL, about 0.92 mg/mL, about 0.93 mg/mL, about 0.94 mg/mL, about 0.95 mg/mL, about 0.96 mg/mL, about 0.97 mg/mL, about 0.98 mg/mL, about 0.99 mg/mL, about 1 mg/mL, about 1.11 mg/ml, about 1.12 mg/ml, about 1.13 mg/ml, about 1.14 mg/ml, about 1.15 mg/ml, about 1.16 mg/ml, about 1.17 mg/ml, about 1.18 mg/ml, about 1.19 mg/ml, about 1.2 mg/ml, about 1.21 mg/ml, about 1.22 mg/ml, about 1.23 mg/ml, about 1.24 mg/ml, about 1.25 mg/ml, about 1.26 mg/ml, about 1.27 mg/ml, about 1.28 mg/ml, about 1.29 mg/ml, about 1.3 mg/mL, about 1.31 mg/mL, about 1.32 mg/mL, about 1.33 mg/mL, about 1.34 mg/mL, about 1.35 mg/mL, about 1.36 mg/mL, about 1.37 mg/mL, about 1.38 mg/mL, about 1.39 mg/mL, about 1.4 mg/ml, about 1.41 mg/ml, about 1.42 mg/ml, about 1.43 mg/ml, about 1.44 mg/ml, about 1.45 mg/ml, about 1.46 mg/ml, about 1.47 mg/ml, about 1.48 mg/ml, about 1.49 mg/ml, about 1.5 mg/ml, about 1.51 mg/ml, about 1.52 mg/ml, about 1.53 mg/ml, about 1.54 mg/ml, about 1.55 mg/ml, about 1.56 mg/ml, about 1.57 mg/ml, about 1.58 mg/ml, about 1.59 mg/ml, about 1.6 mg/mL, about 1.61 mg/mL, about 1.62 mg/mL, about 1.63 mg/mL, about 1.64 mg/mL, about 1.65 mg/mL, about 1.66 mg/mL, about 1.67 mg/mL, about 1.68 mg/mL, about 1.69 mg/mL, about 1.7 mg/ml, about 1.71 mg/ml, about 1.72 mg/ml, about 1.73 mg/ml, about 1.74 mg/ml, about 1.75 mg/ml, about 1.76 mg/ml, about 1.77 mg/ml, about 1.78 mg/ml, about 1.79 mg/ml, about 1.8 mg/ml, about 1.81 mg/ml, about 1.82 mg/ml, about 1.83 mg/ml, about 1.84 mg/ml, about 1.85 mg/ml, about 1.86 mg/ml, about 1.87 mg/ml, about 1.88 mg/ml, about 1.89 mg/ml, about 1.9 mg/mL, about 1.91 mg/mL, about 1.92 mg/mL, about 1.93 mg/mL, about 1.94 mg/mL, about 1.95 mg/mL, about 1.96 mg/mL, about 1.97 mg/mL, about 1.98 mg/mL, about 1.99 mg/mL, or about 2 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 1.65 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 1.82 mg/ml in the oral liquid formulation. In some embodiments, citric acid is present in about 0.82 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 2 to about 3.5 mg/ml in the oral liquid formulation. In other embodiments, citric acid is present in about 2 mg/mL, about 2.05 mg/mL, about 2.1 mg/mL, about 2.15 mg/mL, about 2.2 mg/mL, about 2.25 mg/mL, about 2.3 mg/mL, about 2.35 mg/mL, about 2.4 mg/mL, about 2.45 mg/mL, about 2.5 mg/mL, about 2.55 mg/mL, about 2.6 mg/mL, about 2.65 mg/mL, about 2.7 mg/mL, about 2.75 mg/mL, about 2.8 mg/mL, about 2.85 mg/mL, about 2.9 mg/mL, about 2.95 mg/mL, about 3 mg/mL, about 3.05 mg/ml, about 3.1 mg/mL, about 3.15 mg/mL, about 3.2 mg/mL, about 3.25 mg/mL, about 3.3 mg/mL, about 3.35 mg/mL, about 3.4 mg/mL, about 3.45 mg/mL, or about 3.5 mg/mL in the oral liquid formulation. In some embodiments, citric acid is present in about 3.3 mg/ml in the oral liquid formulation.

In some embodiments, citric acid is present in about 10% w/w to about 50% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, about 21% w/w, about 22% w/w, about 23% w/w, about 24% w/w, about 25% w/w, about 26% w/w, about 27% w/w, about 28% w/w, about 29% w/w, about 30% w/w, about 31% w/w, about 32% w/w, about 33% w/w, about 34% w/w, about 35% w/w, about 36% w/w, about 37% w/w, about 38% w/w, about 39% w/w, about 40% w/w, about 41% w/w, about 42% w/w, about 43% w/w, about 44% w/w, about 45% w/w, about 46% w/w, about 47% w/w, about 48% w/w, about 49% w/w, about 50% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 45% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 31% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 35% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 19% w/w of the solids in the oral liquid formulation.

In some embodiments, citric acid is present in about 1% w/w to about 5% w/w of the solids in the oral liquid formulation. In other embodiments, citric acid is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.1% w/w, about 4.2% w/w, about 4.3% w/w, about 4.4% w/w, about 4.5% w/w, about 4.6% w/w, about 4.7% w/w, about 4.8% w/w, about 4.9% w/w, or about 5% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 2.1% w/w of the solids in the oral liquid formulation. In some embodiments, citric acid is present in about 1.6% w/w of the solids in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 0.1 to about 0.8 mg/ml in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in the oral liquid formulation is about 0.1 mg/mL, about 0.11 mg/mL, about 0.12 mg/mL, about 0.13 mg/mL, about 0.14 mg/mL, about 0.15 mg/ml, about 0.16 mg/mL, about 0.17 mg/mL, about 0.18 mg/mL, about 0.19 mg/mL, about 0.2 mg/ml, about 0.21 mg/ml, about 0.22 mg/ml, about 0.23 mg/ml, about 0.24 mg/ml, about 0.25 mg/ml, about 0.26 mg/ml, about 0.27 mg/ml, about 0.28 mg/ml, about 0.29 mg/ml, about 0.3 mg/ml, about 0.31 mg/ml, about 0.32 mg/ml, about 0.33 mg/ml, about 0.34 mg/ml, about 0.35 mg/ml, about 0.36 mg/ml, about 0.37 mg/ml, about 0.38 mg/ml, about 0.39 mg/ml, about 0.4 mg/ml, about 0.41 mg/ml, about 0.42 mg/ml, about 0.43 mg/ml, about 0.44 mg/ml, about 0.45 mg/ml, about 0.46 mg/ml, about 0.47 mg/ml, about 0.48 mg/ml, about 0.49 mg/ml, about 0.5 mg/ml, about 0.51 mg/ml, about 0.52 mg/ml, about 0.53 mg/ml, about 0.54 mg/ml, about 0.55 mg/ml,

about 0.56 mg/ml, about 0.57 mg/ml, about 0.58 mg/ml, about 0.59 mg/ml, about 0.6 mg/ml, about 0.61 mg/ml, about 0.62 mg/ml, about 0.63 mg/ml, about 0.64 mg/ml, about 0.65 mg/ml, about 0.66 mg/ml, about 0.67 mg/ml, about 0.68 mg/ml, about 0.69 mg/ml, about 0.7 mg/ml, about 0.71 mg/ml, about 0.72 mg/ml, about 0.73 mg/ml, about 0.74 mg/ml, about 0.75 mg/ml, about 0.76 mg/ml, about 0.77 mg/ml, about 0.78 mg/ml, about 0.79 mg/ml, or about 0.8 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.75 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.35 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.2 mg/ml in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 0.15 mg/ml in the oral liquid formulation.

In some embodiments, sodium citrate dihydrate is present in about 1% w/w to about 15% w/w of the solids in the oral liquid formulation. In other embodiments, sodium citrate dihydrate is present in about 1% w/w, about 1.1% w/w, about 1.2% w/w, about 1.3% w/w, about 1.4% w/w, about 1.5% w/w, about 1.6% w/w, about 1.7% w/w, about 1.8% w/w, about 1.9% w/w, about 2% w/w, about 2.1% w/w, about 2.2% w/w, about 2.3% w/w, about 2.4% w/w, about 2.5% w/w, about 2.6% w/w, about 2.7% w/w, about 2.8% w/w, about 2.9% w/w, about 3% w/w, about 3.1% w/w, about 3.2% w/w, about 3.3% w/w, about 3.4% w/w, about 3.5% w/w, about 3.6% w/w, about 3.7% w/w, about 3.8% w/w, about 3.9% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 10.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 7.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 4.5% w/w of the solids in the oral liquid formulation. In some embodiments, sodium citrate dihydrate is present in about 2.9% w/w of the solids in the oral liquid formulation.

In other embodiments, sodium citrate dihydrate is not added to the formulation.

Additional Excipients

In further embodiments, the enalapril liquid formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant. In some embodiments the glidant is not colloidal silicon dioxide.

In another embodiment, the enalapril liquid formulation comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. In some embodiments, the enalapril liquid formulation described herein comprises a mixed berry flavoring agent. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril liquid formulation comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, FD&C Green No. 5, FD&C Orange No. 5. caramel, ferric oxide and mixtures thereof.

Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.). In certain embodiments, the enalapril liquid formulation comprises a thickener.

Additional excipients are contemplated in the enalapril liquid formulation embodiments. These additional excipients are selected based on function and compatibility with the enalapril liquid formulations described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

Stability

The main enalapril degradants are enalapril diketopiperazine and enalaprilat.

The enalapril oral liquid formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refers to enalapril oral liquid formulations having about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril oral liquid formulations have about 5% w/w, about 4% w/w,

about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril oral liquid formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril oral liquid formulations have about 1% w/w total impurities or related substances.

At refrigerated condition, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 9 months, at least 12 months, at least 15 months, at least 18 months, at least 24 months, at least 30 months and at least 36 months. In some embodiments, refrigerated condition is 5±3° C. In some embodiments, refrigerated condition is about 2° C., about 2.1° C., about 2.2° C., about 2.3° C., about 2.4° C., about 2.5° C., about 2.6° C., about 2.7° C., about 2.8° C., about 2.9° C., about 3° C., about 3.1° C., about 3.2° C., about 3.3° C., about 3.4° C., about 3.5° C., about 3.6° C., about 3.7° C., about 3.8° C., about 3.9° C., about 4° C., about 4.1° C., about 4.2° C., about 4.3° C., about 4.4° C., about 4.5° C., about 4.6° C., about 4.7° C., about 4.8° C., about 4.9° C., about 5° C., about 5.1° C., about 5.2° C., about 5.3° C., about 5.4° C., about 5.5° C., about 5.6° C., about 5.7° C., about 5.8° C., about 5.9° C., about 6° C., about 6.1° C., about 6.2° C., about 6.3° C., about 6.4° C., about 6.5° C., about 6.6° C., about 6.7° C., about 6.8° C., about 6.9° C., about 7° C., about 7.1° C., about 7.2° C., about 7.3° C., about 7.4° C., about 7.5° C., about 7.6° C., about 7.7° C., about 7.8° C., about 7.9° C., or about 8° C. At accelerated conditions, the enalapril oral liquid formulations described herein are stable for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months or at least 12 months. Accelerated conditions for the enalapril oral liquid formulations described herein include temperature and/or relative humidity (RH) that are at or above ambient levels (e.g. 25±5° C.; 55±10% RH). In some instances, an accelerated condition is at about 25° C., about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 55% RH, about 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Enalapril Oral Powder Formulation

In another aspect, enalapril oral liquid formulations described herein are prepared from the reconstitution of an enalapril powder formulation. In some embodiments, the enalapril powder formulation comprising enalapril, a sweetener, a preservative, and optionally an excipient is dissolved in water, a buffer, other aqueous solvent, or a liquid to form an enalapril oral liquid formulation. In one embodiment, the sweetening agent is sucralose. In one embodiment, the sweetener is not mannitol. In one embodiment, the sweetening agent is xylitol. In another embodiment, the preservative is sodium benzoate. In one embodiment, the preservative is a paraben preservative. In one aspect, the enalapril powder formulation described herein comprises enalapril, sucralose, and sodium benzoate. In some embodiments, the enalapril powder formulation herein further comprises a flavoring agent. In some embodiments, the enalapril powder formulation herein further comprises one or more buffering agents.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w to about 30% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.5% w/w, about 1% w/w, about 1.5% w/w, about 2% w/w, about 2.5% w/w, about 3% w/w, about 3.5% w/w, about 4% w/w, about 4.5% w/w, about 5% w/w, about 5.5% w/w, about 6% w/w, about 6.5% w/w, about 7% w/w, about 7.5% w/w, about 8% w/w, about 8.5% w/w, about 9% w/w, about 9.5% w/w, about 10% w/w, about 10.5% w/w, about 11% w/w, about 11.5% w/w, about 12% w/w, about 12.5% w/w, about 13% w/w, about 13.5% w/w, about 14% w/w, about 14.5% w/w, about 15% w/w, about 15.5% w/w, about 16% w/w, about 16.5% w/w, about 17% w/w, about 17.5% w/w, about 18% w/w, about 18.5% w/w, about 19% w/w, about 19.5% w/w, about 20% w/w, about 20.5% w/w, about 21% w/w, about 21.5% w/w, about 22% w/w, about 22.5% w/w, about 23% w/w, about 23.5% w/w, about 24% w/w, about 24.5% w/w, about w/w, about 25.5% w/w, about 26% w/w, about 26.5% w/w, about 27% w/w, about 27.5% w/w, about 28% w/w, about 28.5% w/w, about 29% w/w, about 29.5% w/w, or about 30% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 10% w/w to about 25% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 13.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 19.5% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 24.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 10.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 14.5% w/w of the powder formulation. In some embodiments, enalapril is present in about 18% w/w of the powder formulation.

In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w to about 1% w/w of the powder formulation. In other embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.1% w/w, about 0.15% w/w, about 0.2% w/w, about 0.25% w/w, about 0.3% w/w, about 0.35% w/w, about 0.4% w/w, about 0.45% w/w, about 0.5% w/w, about 0.55% w/w, about 0.6% w/w, about 0.65% w/w, about 0.7% w/w, about 0.75% w/w, about 0.8% w/w, about 0.85% w/w, about 0.9% w/w, about 0.95% w/w, or about 1% w/w of the powder formulation. In some embodiments, enalapril or a pharmaceutically acceptable salt thereof, is present in about 0.4% w/w to about 0.7% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.45% w/w of the powder formulation. In some embodiments, enalapril maleate is present in about 0.6% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.4% w/w of the powder formulation. In some embodiments, enalapril is present in about 0.5% w/w of the powder formulation.

Various amounts and concentrations of other components (sweeteners, buffers, preservatives, and the like) in the enalapril powder formulations are found in the previous section describing the amounts and concentrations for the analogous enalapril oral liquid formulations. For example, in

some embodiments where sucralose is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation; in an analogous enalapril powder formulation, sucralose would be about 1% w/w to about 30% w/w in the powder formulation. In some embodiments where sodium benzoate is present in about 1% w/w to about 30% w/w of the solids in the oral liquid formulation, in an analogous enalapril powder formulation sodium benzoate is present in about 1% w/w to about 30% w/w in the powder formulation.

Liquid vehicles suitable for the enalapril powder formulations to be reconstituted into an oral solution described herein are selected for a particular oral liquid formulation (solution, suspension, etc.) as well as other qualities such as clarity, toxicity, viscosity, compatibility with excipients, chemical inertness, palatability, odor, color and economy. Exemplary liquid vehicles include water, ethyl alcohol, glycerin, propylene glycol, syrup (sugar or other sweetener based, e.g., Ora-Sweet® SF sugar-free flavored syrup), juices (apple, grape, orange, cranberry, cherry, tomato and the like), other beverages (tea, coffee, soft drinks, milk and the like), oils (olive, soybean, corn, mineral, castor and the like), and combinations or mixtures thereof. Certain liquid vehicles, e.g., oil and water, can be combined together to form emulsions. In some embodiments, water is used for as a vehicle for a enalapril oral liquid formulation. In other embodiments, a syrup is used for as a vehicle for a enalapril oral liquid formulation. In yet other embodiments, a juice is used for as a vehicle for a enalapril oral liquid formulation.

Buffering agents maintain the pH of the liquid enalapril formulation. Non-limiting examples of buffering agents include, but are not limited to sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include citric acid, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. Some buffering agents also impart effervescent qualities when a powder is reconstituted in a solution.

In some embodiments, the reconstituted oral liquid formulation comprises a buffer. In some embodiments, the buffer comprises citric acid and sodium citrate.

In further embodiments, the enalapril powder formulation described herein comprises additional excipients including, but not limited to, glidants, flavoring agents, coloring agents and thickeners. Additional excipients such as bulking agents, tonicity agents and chelating agents are within the scope of the embodiments.

Glidants are substances that improve flowability of a powder. Suitable glidants include, but are not limited to, calcium phosphate tribasic, calcium silicate, cellulose (powdered), colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc and the like. In some embodiments, the enalapril powder formulations described herein comprise a glidant.

In another embodiment, the enalapril powder formulation described herein comprises a flavoring agent or flavorant to enhance the taste or aroma of the formulation in liquid form. Suitable natural or synthetic flavoring agents can be selected from standard reference books, for example Fenaroli's Handbook of Flavor Ingredients, 3rd edition (1995). Non-limiting examples of suitable natural flavors, some of which can readily be simulated with synthetic agents or combinations thereof, include almond, anise, apple, apricot, bergamot, blackberry, blackcurrant, blueberry, cacao, caramel, cherry, cinnamon, clove, coffee, coriander, cranberry, cumin, dill, eucalyptus, fennel, fig, ginger, grape, grapefruit, guava, hop, lemon, licorice, lime, malt, mandarin, molasses, nutmeg, mixed berry, orange, peach, pear, peppermint, pineapple, raspberry, rose, spearmint, strawberry, tangerine, tea, vanilla, wintergreen, etc. Also useful, particularly where the formulation is intended primarily for pediatric use, is tutti-frutti or bubblegum flavor, a compounded flavoring agent based on fruit flavors. Presently preferred flavoring agents include anise, cinnamon, cacao, orange, peppermint, cherry (in particular wild cherry), grape, bubblegum, vanilla, and mixed berry. Flavoring agents can be used singly or in combinations of two or more.

In further embodiments, the enalapril powder formulation described herein comprises a coloring agent for identity and/or aesthetic purposes. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

In further embodiments, the enalapril powder formulation described herein comprises a thickener. Thickeners impart viscosity or weight to the resultant liquid forms from the enalapril formulation described herein. Exemplary thickeners include dextrin, cellulose derivatives (carboxymethylcellulose and its salts, ethylcellulose, hydroxyethyl cellulose, methylcellulose, hypromellose, and the like) starches, pectin, polyethylene glycol, polyethylene oxide, trehalose and certain gums (xanthan gum, locust bean gum, etc.).

Additional excipients are contemplated in the enalapril powder formulation embodiments. These additional excipients are selected based on function and compatibility with the the enalapril powder formulation described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, (Easton, Pa.: Mack Publishing Co 1975); Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, N.Y.: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

In some embodiments, the enalapril oral liquid formulation prepared from the powder formulations described herein are homogenous. Homogenous liquids as used herein refer to those liquids that are uniform in appearance, identity, consistency and drug concentration per volume. Non-homogenous liquids include such liquids that have varied coloring, viscosity and/or aggregation of solid particulates, as well as non-uniform drug concentration in a given unit volume. Homogeneity in liquids are assessed by qualitative identification or appearance tests and/or quantitative HPLC testing or the like. The mixing methods and excipients described herein are selected to impart a homogenous quality to a resultant enalapril oral liquid formulation.

Mixing methods encompass any type of mixing that result in a homogenous enalapril oral liquid formulation. In some

embodiments, a quantity of an enalapril powder formulation is added to a liquid vehicle and then mixed by a stirring, shaking, swirling, agitation element or a combination thereof. In certain instances, a fraction of a enalapril powder formulation (i.e., one-half, one-third, one-fourth, etc.) is added to a liquid vehicle, mixed by stirring, shaking, swirling, agitation or a combination thereof, and the subsequent powder fraction(s) is added and mixed. In other embodiments, a liquid vehicle is added to an enalapril powder formulation in a container, for example, a bottle, vial, bag, beaker, syringe, or the like. The container is then mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof. In certain instances, a fractional volume of the liquid vehicle (i.e., one-half, one-third, one-fourth volume, etc.) is added to a enalapril powder formulation in a container, mixed by stirring, shaking, swirling, agitation, inversion or a combination thereof and the subsequent liquid fraction(s) is added and mixed. In certain instances, a one-half fractional volume of the liquid vehicle is added to an enalapril powder formulation in a container and mixing by shaking; the other one-half fractional volume of the liquid vehicle is then subsequently added and mixed. In any of the above embodiments, mixing (i.e., stirring, shaking, swirling, agitation, inversion or a combination thereof) occurs for a certain time intervals such as about 10 seconds, about 20 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 120 seconds, about 2.5 minutes, about 3 minutes, about 3.5 minutes, about 4 minutes, or about 5 minutes. In embodiments, where there are two or more mixing steps, the time intervals for each mixing can be the same (e.g., 2×10 seconds) or different (e.g., 10 seconds for first mixing and 20 seconds for second mixing). In any of the above embodiments, a enalapril oral liquid formulation is allowed to stand for a period of time such as about 10 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours or about 2 hours, to allow any air bubbles resultant from any of the mixing methods to dissipate.

Stability of Enalapril Powder Formulation

The enalapril powder formulations described herein are stable in various storage conditions including refrigerated, ambient and accelerated conditions. Stable as used herein refer to enalapril powder formulations having about 95% or greater of the initial enalapril amount and 5% w/w or less total impurities or related substances at the end of a given storage period. The percentage of impurities is calculated from the amount of impurities relative to the amount of enalapril. Stability is assessed by HPLC or any other known testing method. In some embodiments, the stable enalapril powder formulations have about 5% w/w, about 4% w/w, about 3% w/w, about 2.5% w/w, about 2% w/w, about 1.5% w/w, about 1% w/w, or about 0.5% w/w total impurities or related substances. In other embodiments, the stable enalapril powder formulations have about 5% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 4% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 3% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 2% w/w total impurities or related substances. In yet other embodiments, the stable enalapril powder formulations have about 1% w/w total impurities or related substances.

At refrigerated and ambient conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 16 weeks, 20 weeks, at least 24 weeks, at least 30 weeks, or at least 36 weeks. At accelerated conditions, in some embodiments, the enalapril powder formulations described herein are stable for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks or at least 12 weeks. Accelerated conditions for the enalapril powder formulations described herein include temperature and/or relative humidity (RH) that are above ambient levels (e.g. 25±4° C.; 55±10% RH). In some instances, an accelerated condition is at about 30° C., about 35° C., about 40° C., about 45° C., about 50° C., about 55° C. or about 60° C. In other instances, an accelerated condition is above 65% RH, about 70% RH, about 75% RH or about 80% RH. In further instances, an accelerated condition is about 40° C. or 60° C. at ambient humidity. In yet further instances, an accelerated condition is about 40° C. at 75±5% RH humidity.

Kits and Articles of Manufacture

For the enalapril powder and liquid formulations described herein, kits and articles of manufacture are also described. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein including an enalapril powder or liquid formulation. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for an enalapril powder or liquid formulation described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use associated with an enalapril powder or liquid formulation. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

Methods

Provided herein, in one aspect, are methods of treatment comprising administration of the enalapril oral liquid formulations described herein to a subject. In some embodiments, the enalapril oral liquid formulations described herein treat hypertension in a subject. Hypertension as used herein includes both primary (essential) hypertension and

secondary hypertension. In certain instances, hypertension is classified in cases when blood pressure values are greater than or equal to 140/90 (systolic/diastolic) mm Hg in a subject. In certain instances, the enalapril oral liquid formulations described herein treat a subject having a blood pressure values are greater than or equal to 140/90 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat primary (essential) hypertension in a subject. In other instances, the enalapril oral liquid formulations described herein treat secondary hypertension in a subject.

In other embodiments, the enalapril oral liquid formulations described herein treat prehypertension in a subject. Prehypertension as used herein refers to cases where a subject's blood pressure is elevated above normal but not to the level considered to be hypertension. In some instances, prehypertension is classified in cases when blood pressure values are 120-139/80-89 mm Hg. In certain instances, the enalapril oral liquid formulations described herein treat a subject having blood pressure values of 120-139/80-89 mm Hg.

In yet other embodiments, the enalapril oral liquid formulations described herein are prophylactically administered to subjects suspected of having, predisposed to, or at risk of developing hypertension. In some embodiments, the administration of enalapril oral liquid formulations described herein allow for early intervention prior to onset of hypertension. In certain embodiments, upon detection of a biomarker, environmental, genetic factor, or other marker, the enalapril oral liquid formulations described herein are prophylactically administered to subjects.

In further embodiments, the enalapril oral liquid formulations described herein treat heart failure (e.g., symptomatic congestive), asymptomatic left ventricular dysfunction, myocardial infarction, diabetic nephropathy and chronic renal failure. In certain instances, the enalapril oral liquid formulations described herein treat symptomatic congestive heart failure. In other instances, the enalapril oral liquid formulations described herein treat asymptomatic left ventricular dysfunction. In further instances, the enalapril oral liquid formulations described herein treat myocardial infarction. In yet further instances, the enalapril oral liquid formulations described herein treat diabetic nephropathy. In yet further instances, the enalapril oral liquid formulations described herein treat chronic renal failure.

Dosing

In one aspect, the enalapril oral liquid formulations are used for the treatment of diseases and conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of enalapril oral liquid formulations in therapeutically effective amounts to said subject.

Dosages of enalapril oral liquid formulations described can be determined by any suitable method. Maximum tolerated doses (MTD) and maximum response doses (MRD) for enalapril and/or enalaprilat can be determined via established animal and human experimental protocols as well as in the examples described herein. For example, toxicity and therapeutic efficacy of enalapril and/or enalaprilat can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Enalapril dosages exhibiting high therapeutic indices are of interest. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Additional relative dosages, represented as a percent of maximal response or of maximum tolerated dose, are readily obtained via the protocols.

In some embodiments, the amount of a given enalapril oral liquid formulation that corresponds to such an amount varies depending upon factors such as the particular enalapril salt or form, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the liquid composition type, the condition being treated, and the subject or host being treated.

In some embodiments, the enalapril oral liquid formulations described herein are provided in a dose per day from about 0.01 mg to 100 mg, from about 0.1 mg to about 80 mg, from about 1 to about 60, from about 2 mg to about 40 mg of enalapril. In certain embodiments, the enalapril oral liquid formulations described herein are provided in a daily dose of about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.2 mg, about 0.4 mg, about 0.6 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 76, mg, about 80 mg, about 85 mg, about 90 mg or about 100 mg, or any range derivable therein. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 1 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 2 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 3 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 4 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 5 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 6 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 7 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 8 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 9 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 10 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 11 mg. In certain instances, the enalapril oral liquid formulations described herein are provided in a dose per day of about 12 mg. The dose per day described herein can be given once per day or multiple times per day in the form of sub-doses given b.i.d., t.i.d., q.i.d., or the like where the number of sub-doses equal the dose per day.

In further embodiments, the daily dosages appropriate for the enalapril oral liquid formulations described herein are from about 0.01 to about 1.0 mg/kg per body weight. In one embodiment, the daily dosages appropriate for the enalapril oral liquid formulations are from about 0.02 to about 0.8 mg/kg enalapril per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations are from about 0.05 to about 0.6 mg/kg per body weight. In another embodiment, the daily dosage appropriate for the enalapril oral liquid formulations is about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.10 mg/kg, about 0.15 mg/kg, about 0.20 mg/kg, about 0.25 mg/kg, about 0.30 mg/kg, about 0.40 mg/kg, about 0.50 mg/kg, or about 0.60 mg/kg.

In other embodiments the enalapril oral liquid formulations are provided at the maximum tolerated dose (MTD) for enalapril and/or enalaprilat. In other embodiments, the amount of the enalapril oral liquid formulations administered is from about 10% to about 90% of the maximum tolerated dose (MTD), from about 25% to about 75% of the MTD, or about 50% of the MTD. In particular embodiments, the amount of the enalapril oral liquid formulations administered is from about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or higher, or any range derivable therein, of the MTD for enalapril and/or enalaprilat.

In further embodiments, the enalapril oral liquid formulations are provided in a dosage that is similar, comparable or equivalent to a dosage of a known enalapril tablet formulation. In other embodiments, the enalapril oral liquid formulations are provided in a dosage that provides a similar, comparable or equivalent pharmacokinetic parameters (e.g., AUC, C_{max}, T_{max}, C_{min}, $T_{1/2}$) as a dosage of a known enalapril tablet formulation. Similar, comparable or equivalent pharmacokinetic parameters, in some instances, refer to within 80% to 125%, 80% to 120%, 85% to 125%, 90% to 110%, or increments therein, of the given values. It should be recognized that the ranges can, but need not be symmetrical, e.g., 85% to 105%.

Administration

Administration of an enalapril oral liquid formulation is at a dosage described herein or at other dose levels and formulations determined and contemplated by a medical practitioner. In certain embodiments, the enalapril oral liquid formulations described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the enalapril oral liquid formulations are administered to a patient already suffering from a disease, e.g., hypertension, in an amount sufficient to cure the disease or at least partially arrest or ameliorate the symptoms, e.g., lower blood pressure. Amounts effective for this use depend on the severity of the disease, previous therapy, the patient's health status, weight, and response to the enalapril formulations, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

In prophylactic applications, the enalapril oral liquid formulations described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, e.g., hypertension. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the risk or susceptibility of developing the particular disease, previous therapy, the patient's health status and response to the enalapril formulations, and the judgment of the treating physician.

In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of an enalapril oral liquid formulations described herein are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease. In other embodiments, administration of an enalapril oral liquid formulation continues until complete or partial response of a disease.

In certain embodiments wherein a patient's status does improve, the dose of an enalapril oral liquid formulation being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

In some embodiments, enalapril oral liquid formulations described herein are administered chronically. For example, in some embodiments, an enalapril oral liquid formulation is administered as a continuous dose, i.e., administered daily to a subject. In some other embodiments, enalapril oral liquid formulations described herein are administered intermittently (e.g. drug holiday that includes a period of time in which the formulation is not administered or is administered in a reduced amount).

In some embodiments an enalapril oral liquid formulation is administered to a subject who is in a fasted state. A fasted state refers to a subject who has gone without food or fasted for a certain period of time. General fasting periods include at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours and at least 16 hours without food. In some embodiments, an enalapril oral liquid formulation is administered orally to a subject who is in a fasted state for at least 8 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 10 hours. In yet other embodiments, an enalapril oral liquid formulation is administered to a subject who is in a fasted state for at least 12 hours. In other embodiments, an enalapril oral liquid formulation is administered to a subject who has fasted overnight.

In other embodiments an enalapril oral liquid formulation is administered to a subject who is in a fed state. A fed state refers to a subject who has taken food or has had a meal. In certain embodiments, an enalapril oral liquid formulation is administered to a subject in a fed state 5 minutes post-meal, 10 minutes post-meal, 15 minutes post-meal, 20 minutes post-meal, 30 minutes post-meal, 40 minutes post-meal, 50 minutes post-meal, 1 hour post-meal, or 2 hours post-meal. In certain instances, an enalapril oral liquid formulation is administered to a subject in a fed state 30 minutes post-meal. In other instances, an enalapril oral liquid formulation is administered to a subject in a fed state 1 hour post-meal. In yet further embodiments, an enalapril oral liquid formulation is administered to a subject with food.

In further embodiments described herein, an enalapril oral liquid formulation is administered at a certain time of day for the entire administration period. For example, an enalapril oral liquid formulation can be administered at a certain time in the morning, in the evening, or prior to bed. In certain instances, an enalapril oral liquid formulation is administered in the morning. In other embodiments, an enalapril oral liquid formulation can be administered at different times of the day for the entire administration period. For example, an enalapril oral liquid formulation can be administered on 8:00 am in the morning for the first day, 12 pm noon for the next day or administration, 4 pm in the afternoon for the third day or administration, and so on.

Further Combinations

The treatment of certain diseases or conditions (e.g., hypertension, heart failure, myocardial infarction and the like) in a subject with an enalapril oral liquid formulation described herein encompass additional therapies and treatment regimens with other agents in some embodiments. Such additional therapies and treatment regimens can include another therapy, e.g., additional anti-hypertensives, for treatment of the particular disease or condition in some embodiments. Alternatively, in other embodiments, additional therapies and treatment regimens include other agents used to treat adjunct conditions associated with the disease or condition or a side effect from the enalapril oral liquid formulation in the therapy.

Additional agents for use in combination with an enalapril oral liquid formulation described herein include, but are not limited to, diuretics (loop, thiazide, potassium-sparing, and the like), beta blockers (metoprolol, propanolol, pronethalol, and the like), alpha blockers (phentolamine, phenoxybenzamine, tamsulosin, prazosin, and the like), mixed alpha and beta blockers (bucindolol, carvedilol, labetalol), calcium channel blockers (dihydropyridines such as nifedipine, amlodipine, etc., dilitazem, verapamil and the like), angiotensin II receptor antagonists (saralasin, lsartan, eprosartin, irbesartan, valsartan, and the like), other ACE inhibitors (captopril, quinapril, ramipril, lisinopril, zofenopril, and the like), aldosterone antagonists (eplerenone, spironolactone and the like), vasodilators (hydralazine and the like) and alpha-2 agonists (clonidine, moxonidine, guanabenz and the like).

Certain Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

The term "about" is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value. The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to "and/or." The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

"Optional" or "optionally" may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

As used herein, the term "therapeutic" means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient. In some embodiments, a therapeutic agent such as enalapril is directed to the treatment and/or the amelioration of, reversal of, or stabilization of the symptoms of hypertension described herein.

"Administering" when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted. Thus, as used herein, the term "administering", when used in conjunction with an enalapril formulation, can include, but is not limited to, providing an enalapril formulation into or onto the target tissue; providing an enalapril formulation systemically to a patient by, e.g., oral administration whereby the therapeutic reaches the target tissue or cells. "Administering" a formulation may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

The term "animal" as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms "patient," "subject" and "individual" are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows. The experimental animal can be an animal model for a disorder, e.g., a transgenic mouse with hypertensive pathology. A patient can be a human suffering from hypertension, or its variants or etiological forms.

By "pharmaceutically acceptable", it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term "pharmaceutical composition" shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

A "therapeutically effective amount" or "effective amount" as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological

or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology). As such, a non-limiting example of a "therapeutically effective amount" or "effective amount" of a formulation of the present disclosure may be used to inhibit, block, or reverse the activation, migration, or proliferation of cells or to effectively treat hypertension or ameliorate the symptoms of hypertension.

The terms "treat," "treated," "treatment," or "treating" as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, "treat," "treated," "treatment," or "treating" includes prophylaxis in some embodiments.

EXAMPLES

Example A: Effect of pH on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table A-1. The pH of each solution was recorded. Five milliliters of each formulation were transferred to each of four 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then one vial removed and analyzed by HPLC at times of zero, ~97 and ~180 hours.

TABLE A-1

Formulation (in mg/mL) of Enalapril Formulations at Varying pH and Citrate Buffer Concentration

	Formulation (mM citrate)					
Component	A1 (50)	A2 (50)	A3 (50)	A4 (50)	A5 (50)	A6 (25)
Enalapril maleate	1.0	1.0	1.0	1.0	1.0	1.0
Mannitol	50	50	50		50	6.0
Xylitol				50		
Citric acid, anhydrous	7.35	5.05	2.55	5.05	5.05	2.76
Sodium citrate, dihydrate	3.45	7.0	10.8	7.0	7.0	3.15
Sodium benzoate	1	1	1	1	1	
Methylparaben sodium					1.75	0.335
Propylparaben sodium						0.095
Potassium sorbate						1
Sucralose	0.75	0.75	0.75	0.75	0.75	0.75
Silicon dioxide						0.075
Mixed berry flavor (powdered)	0.5	0.5	0.5	0.5	0.5	0.5
Water	qs	qs	qs	qs	qs	qs
pH	3.4	4.4	5.2	4.4	4.5	4.4

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table A-2.

TABLE A-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

	Formulation					
Hours at 60° C.	A1	A2	A3	A4	A5	A6
Enalapril Diketopiperazine						
0	0.04	0.03	0.03	0.03	0.03	0.03
97	3.10	0.88	0.33	0.86	0.70	0.53
180	6.21	1.77	0.75	1.73	1.43	1.07
Enalaprilat						
0	0.09	0.15	0.29	0.14	0.16	0.12
97	5.20	16.9	47.4	16.1	20.3	15.6
180	9.94	34.8	113	33.5	42.2	31.7

Example B: Effect of Buffer Concentration on the Formation of Degradants in Enalapril Formulations at 60° C.

Formulations were prepared containing enalapril maleate according to Table B-1. The pH of each solution was measured and adjusted as needed to pH 3.3 with ~1N HCl or ~0.5N NaOH. Five milliliters of each formulation were

transferred to each of six 3-dram glass screw-capped vials with Teflon inserts in the caps. The vials were placed into a 60° C. heating chamber then two vials were removed and analyzed by HPLC at times of zero, ~66 and ~139 hours.

TABLE B-1

Formulation (in mg/mL) of Enalapril Maleate Formulations at Varying Citrate Buffer Concentrations

Component	Formulation B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril maleate	1.0	1.0	1.0
Citric acid, anhydrous	0.82	1.65	3.29
Sodium citrate, anhydrous	0.19	0.38	0.75
Sodium benzoate	1.0	1.0	1.0
Sucralose	0.7	0.7	0.7
Mixed berry flavor (powdered)	0.5	0.5	0.5
Water	qs	qs	qs
pH	3.3	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the two main degradants in the samples, enalapril diketopiperazine and enalaprilat, are provided in Table B-2.

TABLE B-2

Primary Degradants Present in the Formulations (% w/w of enalapril maleate)

Hours at 60° C.	Formulation B1 (5 mM citrate)	B2 (10 mM citrate)	B3 (20 mM citrate)
Enalapril Diketopiperazine			
0	0.01	0.01	0.01
66	1.57	1.63	1.79
139	3.70	3.94	4.24
Enalaprilat			
0	0.00	0.00	0.00
66	2.98	2.88	3.19
139	5.28	5.23	5.69

Example C: Stability of Enalapril Maleate Formulations Containing Paraben Preservatives

Powder formulations were prepared according to Table C-1. All components in each formulation except mannitol or xylitol were added to a 2.5 liter polypropylene screw capped bottle. The bottle was mixed by inversion in a Turbula® mixer for 5 minutes. The mannitol or xylitol was then added and the components mixed for 5 minutes, then the other half of the mannitol or xylitol was added and a final mix of 5 minutes was completed.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE C-1

Composition of Enalapril Maleate Formulations

Component	C1	C2	C3	C4	C5
Powder Formulation (grams)					
Enalapril maleate	12.3	12.3	8.86	2.16	2.16
Mannitol	74.4	74.4	394.0		
Xylitol				96.6	93.7
Citric acid, anhydrous	28.6	35.6	28.4	5.40	5.40
Sodium citrate, anhydrous	24.5	14.7	7.73	4.10	4.10
Sodium methylparaben	4.17	4.17	8.86	2.16	2.16
Sodium propylparaben	1.10	1.10			
Potassium sorbate	12.3	12.3			
Sodium benzoate			8.86	2.16	2.16
Xanthan Gum					1.62
Colloidal silicon dioxide	0.859	0.859	4.43		1.08
Sucralose	9.20	9.20	6.64	1.62	1.62
Mixed berry flavor	6.13	6.13	4.43	1.08	1.08
Total solids	173.5	170.7	472.3	115.2	115.2
Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Mannitol	6.07	6.07	44.5		
Xylitol				44.7	43.4
Citric acid, anhydrous	2.33	2.90	3.21	2.50	2.50
Sodium citrate, anhydrous	2.00	1.20	0.87	1.90	1.90
Sodium methylparaben	0.34	0.34	1.00	1.00	1.00
Sodium propylparaben	0.09	0.09	1.00		
Potassium sorbate	1.00	1.00			
Sodium benzoate			1.00	1.00	1.00
Xanthan Gum					0.75
Colloidal silicon dioxide	0.07	0.07	0.50		0.50
Sucralose	0.75	0.75	0.75	0.75	0.75
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
pH (measured)	4.4	3.8	3.7	4.4	4.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table C-2.

TABLE C-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage ° C.	Storage Weeks	Formulation C1	C2	C3	C4	C5
			Liquid Formulations				
Diketopiperazine	5	0	0.03	0.04	0.04	0.02	0.02
		4	0.02	0.03	0.03	0.03	0.02
		8	0.03	0.04	0.04		
	19-23	0	0.03	0.04	0.04	0.02	0.02
		4	0.05	0.09	0.11	0.05	0.04
		8	0.08	0.17	0.19		

TABLE C-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)							
	Storage		Formulation				
	° C.	Weeks	C1	C2	C3	C4	C5
			Liquid Formulations				
	40	0	0.03	0.04	0.04	0.02	0.02
		4	0.35	0.91	1.10	0.31	0.21
		8	0.65	1.80	2.05		
Enalaprilat	5	0	0.18	0.14	0.12	0.13	0.19
		4	0.18	0.15	0.12	0.43	0.53
		8	0.55	0.38	0.34		
	19-23	0	0.18	0.14	0.12	0.13	0.19
		4	1.35	0.83	0.80	1.75	2.29
		8	3.34	2.06	1.98		
	40	0	0.18	0.14	0.12	0.13	0.19
		4	10.49	6.08	6.11	12.30	16.14
		8	24.37	14.12	14.22		

Example D: Stability of Enalapril Maleate Formulations Containing Benzoate Preservative

Powder formulations were prepared according to Table D-1. All components in each formulation except enalapril maleate and mannitol or xylitol were blended with a mortar and pestle. The enalapril maleate was then triturated with the blend. The xylitol or mannitol was then triturated into the blend using a geometric dilution technique.

One liter of solution formulation was prepared for each formulation by adding an appropriate amount of each powdered formulation to a 1 liter volumetric flask and adding about 500 mL water. The powder was dissolved with mixing then the contents of the flask were brought to 1 liter with additional water. The amount of powder to add was determined such that the final concentration of enalapril maleate was 1.0 mg/mL. Fifty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

TABLE D-1

Composition of Enalapril Maleate Formulations						
Component	D1	D2	D3	D4	D5	D6
	Powder Formulation (grams)					
Enalapril maleate	3.63	3.63	3.63	3.63	8.86	2.16
Xylitol	537.2	176.1		537.2		
Mannitol			319.4		401.2	98.9
Citric acid, anhydrous	11.9	11.9	11.9	10.4	26.6	6.48
Sodium citrate, anhydrous	2.72	2.72	2.72	4.86	11.3	2.76
Sodium benzoate	3.63	3.63	3.63	3.63	8.86	2.16
Rebalance X60 (sucralose and maltodextrin)		10.9				
Sucralose					6.64	1.62
Saccharin sodium			7.26			
Colloidal silicon dioxide					4.43	
Mixed berry flavor	1.82	1.82	1.82	1.82	4.43	1.08
Total solids	561	211	350.	561	472.3	115.2
	Liquid Formulations (mg/mL)					
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	148.0	48.5		148.0		
Mannitol			88.0		45.3	45.8
Citric acid, anhydrous	3.29	3.29	3.29	2.85	3.00	3.00
Sodium citrate, anhydrous	0.75	0.75	0.75	1.34	1.28	1.28
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Rebalance X60 (sucralose and maltodextrin)		3.00				
Sucralose					0.75	0.75
Saccharin sodium			2.00			
Colloidal silicon dioxide					0.50	
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50	0.50
pH (measured)	3.2	3.2	3.4	3.7	3.6	3.6

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table D-2.

TABLE D-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	D1	D2	D3	D4	D5	D6
			Liquid Formulations					
Diketopiperazine	5	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.07	0.03	0.05	0.05	0.03	
		8	0.11	0.06	0.08	0.08	0.05	
		12	0.08	0.04	0.06	0.06		
		26	0.11	0.07	0.09	0.07		
	19-23	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	0.27	0.21	0.24	0.16	0.12	0.12
		8	0.50	0.41	0.47	0.30	0.21	0.22
		12	0.62	0.52	0.58	0.35		
		26	1.39	1.20	1.33	0.76		
	40	0	0.04	0.02	0.03	0.03	0.04	0.04
		4	2.87	2.32	2.73	1.57	1.21	1.13
		8	5.13	4.42	5.44	2.97	2.23	2.16
		12	6.86	5.90	6.90	3.91		
		26	13.63	12.18	13.56	7.74		
Enalaprilat	5	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.15	0.12	0.06	0.17	0.13	
		8	0.22	0.19	0.22	0.27	0.34	
		12	0.20	0.17	0.19	0.22		
		8	0.32	0.30	0.30	0.39		
	19-23	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	0.69	0.66	0.69	0.86	0.74	0.76
		8	1.38	1.33	1.41	1.68	1.83	1.82
		12	1.71	1.68	1.73	2.15		
		26	3.63	3.61	3.59	4.55		
	40	0	0.03	0.02	0.03	0.03	0.13	0.14
		4	4.76	4.42	4.76	6.45	5.55	5.24
		8	8.95	8.64	9.61	12.94	12.73	12.18
		12	11.01	10.64	11.41	16.16		
		26	17.18	17.11	18.30	27.36		

Example E: Stability of Solution Formulations of Enalapril Maleate

Solution formulations were prepared according to Table E-1. Thirty milliliter aliquots of each formulation were placed into HDPE bottles. The bottles were screw-capped and placed into storage at 5° C.±3° C., at room temperature (19-23° C.) and at 40° C.±2° C. At various times, bottles were removed from the storage condition and analyzed.

Composition of Enalapril Maleate Formulations (mg/mL)

Component	E1	E2	E3	E4	E5	E6
Enalapril maleate	1.00	1.00	1.00	1.00	1.00	1.00
Xylitol	150	200		150		

-continued

Composition of Enalapril Maleate Formulations (mg/mL)

Component	E1	E2	E3	E4	E5	E6
Citric acid anhydrous	3.29	3.29	3.29	3.29	1.65	0.82
Sodium citrate anhydrous	0.75	0.75	0.75	0.75	0.38	0.19
Sodium benzoate	1.00	1.00	1.00	1.00	1.00	1.00
Sucralose			0.70		0.70	0.70
Mixed berry flavor	0.50		0.50	0.50	0.50	0.50
Water	qs	qs	qs	qs	qs	qs
pH (measured)	3.3	3.3	3.3	3.4	3.3	3.3

qs = sufficient quantity

The results of the HPLC analysis for the diketopiperazine and enalaprilat degradants in the samples are provided in Table E-2.

TABLE E-2

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
Diketopiperazine	5	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.04	0.04	0.05	0.04	0.03	0.03
		8	0.04	0.04	0.04	0.04	0.03	0.03
		12	0.05	0.05	0.04	0.05	0.04	0.04
		26	0.07	0.06	0.05	0.06	0.05	0.05
		52					0.15	0.14
		62	0.18	0.18	0.16	0.14		
	19-23	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	0.22	0.23	0.21	0.20	0.16	0.15
		8	0.35	0.35	0.32	0.31	0.29	0.28

TABLE E-2-continued

Degradant Content After Storage (% w/w of enalapril maleate)

	Storage		Formulation					
	° C.	Weeks	E1	E2	E3	E4	E5	E6
		12	0.58	0.59	0.53	0.51	0.48	0.45
		26	1.10	1.10	1.00	0.95	0.97	0.92
		52					2.30	2.15
		62	3.02	3.04	2.75	2.64		
	40	0	0.01	0.01	0.01	0.01	0.01	0.01
		4	2.65	2.71	2.60	2.42	1.76	1.68
		8	4.02	3.99	3.99	3.62	3.37	3.13
		12	6.72	6.42	6.47	6.00	5.53	5.29
Enalaprilat	5	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.07	0.09	0.10	0.11	0.07	0.08
		8	0.12	0.14	0.10	0.13	0.09	0.08
		12	0.16	0.15	0.15	0.17	0.14	0.11
		26	0.31	0.30	0.29	0.31	0.27	0.24
		52					0.54	0.46
		62	0.75	0.75	0.74	0.71		
	19-23	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	0.65	0.65	0.68	0.70	0.50	0.46
		8	1.17	1.19	1.20	1.23	1.03	0.95
		12	1.67	1.69	1.72	1.80	1.30	1.21
		26	3.36	3.38	3.42	3.57	3.07	2.90
		52					6.32	5.88
		62	7.99	8.02	8.04	8.57		
	40	0	0.00	0.00	0.01	0.02	0.00	0.00
		4	4.85	4.93	5.19	5.42	3.33	3.25
		8	8.08	8.06	8.56	9.01	6.65	6.35
		12	10.70	10.48	11.01	11.97	8.14	7.96

Example F: Effect of pH on the Formation of Degradants in Enalapril Formulations at 5° C. and 19-23° C.

The content of enalapril diketopiperazine and enalaprilat that were formed after 8 weeks of storage for formulations C1-C3 and D1-D5 are plotted in FIG. **1** (5° C.±3° C.) and FIG. **2** (19-23° C. storage). These formulations all contained 20 mM total citrate buffer content, but with varying pH. The general effects of formulation pH on the formation of the two main enalapril degradants are shown.

Example G: Antimicrobial Effectiveness Testing of Enalapril Maleate Formulations at pH 3.3

Enalapril formulations were prepared containing differing amounts of the antimicrobial preservative, sodium benzoate. The formulations were then tested for antimicrobial effectiveness (AET) according to the procedures in the 2014 United States Pharmacopeia 37, Chapter <51> for category 3 products. The formulation of the formulations and the AET results are included in Table G-1.

TABLE G-1

Formulation and AET Testing Results

	Formulation				
	G1	G2	G3	G4	G5
	Formulation (mg/mL)				
Enalapril maleate	1.00	1.00	1.00	1.00	1.00
Xylitol	150	150	150	150	
Sucralose					0.70
Citric acid, anhydrous	1.64	1.64	1.64	1.64	1.80
Sodium citrate, anhydrous	0.322	0.322	0.322	0.322	
Sodium citrate, dihydrate					0.165

TABLE G-1-continued

Formulation and AET Testing Results

	Formulation				
	G1	G2	G3	G4	G5
Sodium benzoate	1.00	0.80	0.60	0.40	1.0
Mixed berry flavor	0.50	0.50	0.50	0.50	0.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	as need to achieve pH				
Measured pH	3.3	3.3	3.3	3.3	3.3
	AET Results				
USP <51>	Pass	Pass	Pass	Pass	Pass

qs = sufficient quantity

Example H: Clinical Trial: Bioavailability Study of 10 mg Enalapril Maleate Oral Solution vs. 10 mg Epaned® Powder for Oral Solution (Reconstituted) Under Fasted Conditions

The objective of this open-label, randomized, two-period, two-treatment, two-way crossover study was to compare the oral bioavailability of a test formulation of 10 mL of enalapril maleate oral solution, 1 mg/mL (formulation E-5), to an equivalent oral dose of the commercially available comparator product, Epaned® (enalapril maleate) Powder for Oral Solution, 1 mg/mL, when administered under fasted conditions in healthy adults.

Study design: Thirty-two healthy adult subjects received a single 10 mL dose of enalapril maleate oral solution, 1 mg/mL, formulation E-5 (Treatment A), in one period and a separate single dose of Epaned Powder for Oral Solution (reconstituted with the supplied Ora-Sweet SF), 1 mg/mL (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours, followed by a 4-hour fast postdose. Each treatment was administered

via a 10 mL oral dosing syringe and followed with 240 mL of room temperature tap water. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose. In addition, during each period, blood samples were obtained prior to and following each dose at selected times through 72 hours postdose. Pharmacokinetic samples were analyzed for enalapril and its metabolite enalaprilat using a validated analytical method; appropriate pharmacokinetic parameters were calculated for each formulation using non-compartmental methods. Blood was also drawn and urine collected for clinical laboratory testing at screening and at the end of the study.

Statistical Methods: The concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantitation (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Actual sample times were used for all pharmacokinetic and statistical analyses. Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals (CIs) of the log-transformed parameters were within 80% to 125% for enalapril and enalaprilat.

Results: A total of 32 subjects participated in the study and 29 of these subjects completed both study periods. Based on the geometric mean ratios of enalapril and enalaprilat AUCs (AUC_{last} and AUC_{inf}), the bioavailability of the enalapril maleate oral solution (formulation E-5) relative to the Epaned Powder for Oral Solution (reconstituted) was approximately 105% to 110%. The geometric mean ratios of enalapril and enalaprilat C_{max} were approximately 115% and 109%, respectively. The 90% CI for comparing the maximum exposure to enalapril and enalaprilat, based on ln (C_{max}), was within the accepted 80% to 125% limits. The 90% CIs for comparing total systemic exposure to enalapril and enalaprilat, based on ln (AUC_{last}) and ln (AUC_{inf}), was within the accepted 80% to 125% limits. Therefore, the test formulation of enalapril maleate oral solution, 1 mg/mL, is bioequivalent to the reference product, Epaned Powder for Oral Solution (reconstituted), 1 mg/mL, under fasted conditions.

While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

What is claimed is:

1. A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;

(iii) a preservative, wherein the preservative is a paraben or a mixture of parabens; and

(iv) water;

wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

2. The stable oral liquid formulation of claim **1**, comprising a sweetener.

3. The stable oral liquid formulation of claim **1**, comprising a flavoring agent.

4. The stable oral liquid formulation of claim **1**, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

5. The stable oral liquid formulation of claim **1**, wherein the buffer concentration is about 10 mM to about 20 mM.

6. The stable oral liquid formulation of claim **1**, wherein the buffer maintains the pH between about 3 and about 4.

7. The stable oral liquid formulation of claim **1**, wherein the buffer maintains the pH at about 3.3.

8. The stable oral liquid formulation of claim **1**, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.

9. The stable oral liquid formulation of claim **1**, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.

10. The stable oral liquid formulation of claim **1**, wherein the preservative is a mixture of parabens.

11. The stable oral liquid formulation of claim **1**, wherein the paraben or the mixture of parabens is methylparaben, ethylparaben, propylparaben, butylparaben, salts thereof, or a combination thereof.

12. The stable oral liquid formulation of claim **1**, wherein the preservative is a mixture of methylparaben and propylparaben.

13. The stable oral liquid formulation of claim **1**, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.

14. The stable oral liquid formulation of claim **1**, wherein the paraben or the mixture of parabens is present at about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation.

15. The stable oral liquid formulation of claim **1**, wherein the paraben or the mixture of parabens is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

16. The stable oral liquid formulation of claim **1**, wherein the paraben or the mixture of parabens is present at about 2% w/w to about 30% w/w of the solids in the oral liquid formulation.

17. The stable oral liquid formulation of claim **1**, wherein the formulation is stable at about 5±3° C. for at least 18 months.

18. The stable oral liquid formulation of claim **1**, wherein the formulation is stable at about 5±3° C. for at least 24 months.

19. A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer to maintain the pH about 4.5 or below, wherein the buffer concentration is about 5 mM to about 20 mM;

(iii) a preservative, wherein the preservative is methylparaben, ethylparaben, propylparaben, butylparaben, or a combination thereof; and

(iv) water;

wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

20. The stable oral liquid formulation of claim **19**, wherein the buffer comprises a citrate, a phosphate, a citrate/phosphate, an acetate, a glycinate, an amino acid, or a tartrate buffer.

21. The stable oral liquid formulation of claim **19**, wherein the buffer concentration is about 10 mM to about 20 mM.

22. The stable oral liquid formulation of claim **19**, wherein the buffer maintains the pH between about 3 and about 4.

23. The stable oral liquid formulation of claim **19**, wherein the buffer maintains the pH at about 3.3.

24. The stable oral liquid formulation of claim **19**, comprising about 1.0 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof.

25. The stable oral liquid formulation of claim **19**, wherein the enalapril or a pharmaceutically acceptable salt or solvate thereof is enalapril maleate.

26. The stable oral liquid formulation of claim **19**, wherein the preservative is a mixture of parabens that are selected from methylparaben, ethylparaben, propylparaben, and butylparaben.

27. The stable oral liquid formulation of claim **19**, wherein the preservative is present at about 0.1 mg/ml to about 2 mg/ml in the oral liquid formulation.

28. The stable oral liquid formulation of claim **19**, wherein the preservative is present at about 1.6 mg/ml to about 2 mg/ml in the oral liquid formulation.

29. The stable oral liquid formulation of claim **19**, wherein the preservative is present at about 0.1 mg/ml to about 0.5 mg/ml in the oral liquid formulation.

30. A stable oral liquid formulation, consisting essentially of:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer to maintain the pH about 4.5 or below;

(iii) a preservative, wherein the preservative is methylparaben, ethylparaben, propylparaben, butylparaben, or a combination thereof; and

(iv) water;

wherein the formulation optionally comprises a sweetener, a flavoring agent, or both;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

* * * * *

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(b)(1) because it contains 13,967 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b)(2).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in 14-point Times New Roman, a proportionally spaced typeface, using Microsoft Word.

Dated: March 22, 2023

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